

Studies of Mortality of Atomic Bomb Survivors. Report 13: Solid Cancer and Noncancer Disease Mortality: 1950–1997

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This continues the series of general reports on mortality in the cohort of atomic bomb survivors followed up by the Radiation Effects Research Foundation. This cohort includes 86,572 people with individual dose estimates, 60% of whom have doses of at least 5 mSv. We consider mortality for solid cancer and for noncancer diseases with 7 additional years of follow-up. There have been 9,335 deaths from solid cancer and 31,881 deaths from noncancer diseases during the 47-year follow-up. Of these, 19% of the solid cancer and 15% of the noncancer deaths occurred during the latest 7 years. We estimate that about 440 (5%) of the solid cancer deaths and 250 (0.8%) of the noncancer deaths were associated with the radiation exposure. The excess solid cancer risks appear to be linear in dose even for doses in the 0 to 150-mSv range. While excess rates for radiation-related cancers increase throughout the study period, a new finding is that relative risks decline with increasing attained age, as well as being highest for those exposed as children as noted previously. A useful representative value is that for those exposed at age 30 the solid cancer risk is elevated by 47% per sievert at age 70. There is no significant city difference in either the relative or absolute excess solid cancer risk. Site-specific analyses highlight the difficulties, and need for caution, in distinguishing between site-specific relative risks. These analyses also provide insight into the difficulties in interpretation and generalization of LSS estimates of age-at-exposure effects. The evidence for radiation effects on noncancer mortality remains strong, with risks elevated by about 14% per sievert during the last 30 years of follow-up. Statistically significant increases are seen for heart disease, stroke, digestive diseases, and respiratory diseases. The noncancer data are consistent with some non-linearity in the dose response owing to the substantial uncertainties in the data. There is no direct evidence of radiation effects for doses less than about 0.5 Sv. While there are no statistically signif-

icant variations in noncancer relative risks with age, age at exposure, or sex, the estimated effects are comparable to those seen for cancer. Lifetime risk summaries are used to examine uncertainties of the LSS noncancer disease findings. © 2003 by

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1. INTRODUCTION

This continues the series of periodic general reports on mortality in the Life Span Study (LSS) cohort of A-bomb survivors followed up by the Radiation Effects Research Foundation (RERF). The present report deals with cancer and noncancer mortality during the period from 1950 through 1997, updating with 7 additional years of follow-up results presented by Pierce *et al.* (1) and Shimizu *et al.* (2). The most recent comprehensive reports on LSS cancer incidence (3, 4) are based on follow-up through 1987. More recently, Pierce and Preston (5) used LSS solid cancer incidence data for the period from 1958 through 1994 in an assessment of low-dose risks. Since in recent years there has been little added information regarding the magnitude or age–time patterns of radiation-associated leukemia risks, and the LSS leukemia mortality and incidence data are similar, it is not considered in the current report but will be dealt with in cancer incidence reports to follow.

The LSS cohort includes a large proportion of atomic bomb survivors who were within 2.5 km of the hypocenters at the time of the bombings, together with a similar-sized age- and sex-matched sample of people who were between 3 and 10 km from the hypocenters where radiation doses were negligible. Individual radiation dose estimates are available for 85% of the cohort members who were within 3 km of the bombs and all of the more distant cohort members. The cohort also includes a sample of Hiroshima and Nagasaki residents who were not in the cities at the time of the bombings. As in most analyses of the LSS, this group was not used here. For most purposes, there is little change in the risk estimates if those beyond 3 km from the bombs are omitted from the analyses.

Earlier reports in this series have clearly demonstrated a radiation dose response for cancer and noncancer mortality

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in the LSS. Furthermore, recent LSS reports and our current analyses indicate that the excess mortality rates will increase throughout the lifetime of the survivors. With 7 additional years of follow-up, the total person years at risk increased by 12% and the number of solid cancer and noncancer disease deaths has increased by about 20%, whereas estimates of the numbers of radiation-associated solid cancer and noncancer disease deaths increased by about 30% and 40%, respectively. In regard to solid cancer, while the study confirms previous estimates of the general levels of radiation risks and clarifies the nature of the response at low doses, the most important additional information concerns age-time patterns in the excess risks. This includes both the possible decline of the excess relative risk with attained age and fundamental difficulties in interpretation of age-at-exposure effects. The noncancer analyses strengthen the evidence for excess mortality rates increasing with time and not limited to high doses.

Reports on thermal neutron activation measured in exposed materials (e.g. refs. 6, 7) were interpreted to mean that the current survivor dosimetry system (DS86) might systematically underestimate neutron doses for those Hiroshima survivors who were more than about 1 km from the hypocenter. These reports have led to an international effort to reassess and improve the system used to compute survivor dose estimates. As a result of these efforts the DS86 system will soon be replaced by a new system (DS02). While it now appears [(8) and R. Young, personal communication] that changes in neutron dose estimates will be modest, the new dosimetry system includes improved methods for the computation of γ -ray doses and better adjustments for the effects of external shielding by factory buildings and local terrain features. These changes will have some modest impact on the estimated excess risk per unit dose and may affect in a minor way inference about the shape of the dose response. However, they should have virtually no effect on apparent variations in the radiation-associated excess risks with age at exposure, attained age, or sex, which are a major focus of the current report.

After describing the study population, the analysis data set, and the analytical methods, we present the solid cancer findings. This presentation begins with an overview that describes the number of radiation-associated excess solid cancer deaths and provides summary information on the shape of dose response, temporal patterns in the excess risks, and some site-specific risk estimates. The overview is followed by presentation of additional details concerning the shape of the solid cancer dose response (Section 3.2) and temporal patterns for the excess solid cancer risks (Section 3.3). Our primary solid cancer risk models are described in Section 3.3. Section 3.4 presents solid cancer lifetime risk estimates together with a discussion of their uncertainties. In Section 3.5 we compare temporal patterns in the excess risks for different types of cancer. Variations in the excess risk with age at exposure and sex as well as issues related to the interpretation of these effects are dis-

cussed in Section 3.6. Noncancer results are presented in Section 4. After a brief summary of the main findings, we present more detailed discussions of the dose response and the impact of selection effects on noncancer risk estimates (Section 4.1), temporal patterns and sex effects (Section 4.2), lifetime risk summaries (Section 4.3), and cause-specific risks (Section 4.4). The paper concludes with comments on generalization of LSS risk estimates, the future course of LSS mortality data, and the relationship of our findings to results from studies of other radiation-exposed populations. The Appendix presents detailed summary risk estimates for a number of specific types of solid cancer.

2. MATERIAL AND METHODS

2.1 Study Population and Follow-up

As in our most recent reports, e.g. (1, 2), the portion of the cohort used comprises 86,572 people who were within 10 km of the hypocenter of the bombs and for whom dose estimates are available. The LSS cohort also includes 7,169 people (almost all of whom were within 3 km) for whom dose estimates are not available and 26,580 local residents who were temporarily away from the cities at the time of the bombings. This latter group has routinely been excluded from LSS mortality and cancer incidence analyses because of concerns about the comparability of their mortality rates to those for the rest of the cohort. Mortality follow-up is carried out through routine checks on the vital status of all surviving cohort members. The legally mandated Japanese family registration (*ko-seki*) system, through which these checks are made, provides complete and timely coverage of mortality for cohort members still residing in Japan and allows us to determine the date of loss to follow-up for migrants. Less than 0.2% of the cohort has been lost to follow-up. Once the fact of death has been determined, information on the underlying cause of death is obtained from death certificates. Details regarding cohort selection and follow-up are given in refs. (9, 10).

This report considers deaths from solid cancers and noncancer diseases. Updated detailed analyses of the risks of leukemia (based on incidence data) and other hematopoietic tumors will be presented elsewhere. Leukemia excess risks are well-characterized in refs. (4) and (11), with no important change in the pattern of the excess risks in recent years. Solid cancers include all malignant neoplasms other than those of the lymphatic and hematopoietic tissue, i.e. codes 140–199 of the ICD, 9th revision (12). The general noncancer disease category includes deaths from all noncancer diseases (9th revision ICD code ranges of 0–139, 240–270 and 290–799) excluding diseases of the blood and blood-forming organs (9th revision ICD code range 280–289) that are considered briefly in Section 4.5. The more specific noncancer disease categories considered here include heart disease, stroke, respiratory diseases, digestive diseases, urinary system diseases, diseases of the nervous and endocrine systems, and infectious diseases. We exclude deaths attributed to tumors that were benign or of uncertain nature (ICD codes 210–239) and do not consider deaths from external causes, such as accidents and suicides or deaths attributed to ill-defined or unknown causes. [See ref. (2) for analyses of radiation risks for these causes.]

For this report, follow-up begins on October 1, 1950 and ends on December 31, 1997. As indicated in Table 1, slightly less than half the cohort was alive at the end of follow-up. Lifetime follow-up is virtually complete for those who were over age 40 at the time of exposure, whereas fewer than 10% of those exposed under the age of 10 have died. About 20% of the 44,771 deaths have been attributed to solid cancer while roughly 70% of the deaths are included in the noncancer disease category considered in this report. Most of the remaining deaths were due to accidents or other external causes (5%) or to hematopoietic cancers (1.3%) including leukemia, lymphoma and myeloma deaths.

TABLE 1
LSS Vital Status and Cause of Death Summary by Age at Exposure as of
January 1, 1998

Age at exposure	People	Alive	Total deaths	Cancer and benign tumors			Noncancer diseases		External causes	Ill-defined or unknown cause
				Solid cancers	Hematopoietic cancers	Other tumors	Blood diseases	Other diseases		
0–9	17,824	91%	1,581	456	56	21	9	664	365	10
10–19	17,558	80%	3,528	1,166	107	45	18	1,704	464	24
20–29	10,883	66%	3,725	1,202	100	52	21	2,136	199	15
30–39	12,266	31%	8,456	2,161	130	112	42	5,672	328	11
40–49	13,491	4%	12,942	2,531	127	110	69	9,639	452	14
50+	14,550	0%	14,539	1,819	62	107	63	12,066	392	30
Total	86,572	48%	44,771	9,335	582	447	222	31,881	2,200	104

2.2 Statistical Methods and the Organization of Data for Analysis

The aim of these statistical analyses is to describe cancer and noncancer death rates as functions of dose, age, sex, age at exposure, birth cohort, and city. The data for these analyses consist of a table of deaths and person-years cross-classified by city, sex, radiation dose to the colon (23 categories, as described below), follow-up period (11 generally 5-year categories), attained age (17 5-year categories from ages 5 through 84 and 85 or more), age at exposure (14 5-year categories for the ages 0 through 69 and 70 or more), and distance from the hypocenter (within 3 km or 3–10 km). The colon doses used for defining the dose categories are the sum of the γ -ray dose estimate and 10 times the neutron dose estimate, adjusted (as described below) to allow for the effects of imprecision in dose estimates. The dose category cut points are: 0.005, 0.02, 0.04, 0.06, 0.08, 0.1, 0.125, 0.15, 0.175, 0.20, 0.25, 0.30, 0.50, 0.75, 1.0, 1.25, 1.5, 1.75, 2.0, 2.5 and 3.0 Sv. The analysis table has about 37,000 cells, each of which contains cause-specific counts of the number of deaths and person-years along with mean values of age, age at exposure, year and weighted organ doses. Analyses for all solid cancers as a group and noncancer diseases are based on colon doses, while analyses for specific cancer types are based on specific organ doses. In some analyses, we distinguish between proximal and distal survivors, where proximal is taken to mean survivors who were within 3 km of the hypocenter at the time of the bombing. Distal survivors received negligible radiation exposures from the bombs, while proximal survivors received doses ranging from less than 1 mSv to several sieverts. Roughly, the mean dose doubles with each 200-m decrease in distance from the hypocenter.

As in previous reports, statistical methods are used to reduce risk estimation bias that results from imprecision in individual dose estimates. A primary issue is that by design the dosimetry system (DS86) does not use information provided by the *survival* of the person. That is, the dosimetry system estimates are based on the assessed survivor location and shielding, and they are intended to be unbiased in the frame of reference of all those *exposed* whether or not they survived. Due to imprecision in assessment of survivor location and shielding, for any particular dose estimate those surviving would tend to have lower true doses than those not surviving—the fact of survival providing additional information about true location and shielding. Thus the DS86 dose estimates should be adjusted upward for proximal *survivors*. These issues are unrelated to whether or not there is individual variation in sensitivity to radiation or non-radiation effects of the bombs. RERF *survivor dose estimates* are modified DS86 estimates computed by applying the dose adjustment factors given in ref. (13) for an assumed coefficient of variation for errors in individual dose estimates of 35%. These adjustments, which are a function of shielded kerma, range from a reduction of about 14% for DS86 estimates near 4 Gy to no change for estimates of 0.7 Gy or less. For 263 people, DS86 shielded kerma estimates were truncated to 4 Gy, with corresponding truncation of organ dose estimates before application of the adjustment factors. The dose categories in the analysis table described above are defined in terms of these adjusted colon dose estimates,

whereas in previous reports they were in terms of unadjusted DS86 estimates. Each cell in the table includes mean adjusted dose estimates for various organs.

Poisson regression methods for rates (14, 15) are used to develop descriptive models for the death rates and to characterize radiation effects on these rates. Aside from the grouping of persons on dose and age-at-exposure categories, these methods are equivalent to analysis of survival times under the approximation that death rates are piecewise constant in age within cells of the summary table. Parameter estimation and inference are carried out using the Epicure software (16). Significance tests and confidence bounds are based on χ^2 approximations to the distribution of likelihood ratio tests.

We make use of general rate (hazard) models for both the excess relative risk (ERR) and the excess absolute rate (EAR). An ERR model has the form

$$\lambda_0(c, s, a, b)[1 + ERR(d, e, s, a)],$$

where $\lambda_0(\cdot)$ is the baseline, or background, cancer or noncancer death rate (i.e. the rate for people with zero dose) and the function $ERR(d, e, s, a)$ describes the relative change in rates associated with dose d allowing for effects of age at exposure (e), sex (s), and attained age (a). In an EAR model, we describe the absolute difference between the rates among those exposed to dose d and the rates among those exposed to zero dose. The general form of an EAR model is

$$\lambda_0(c, s, a, b) + EAR(d, e, s, a).$$

The background rate is taken to depend on attained age, year of birth (b), sex and city (c). Although the background rates can be dealt with by stratification, in this report we make use of the parametric models described below.

The ERR and EAR functions are described as parametric functions of the form $\rho(d)e(e, s, a)$ in which $\rho(d)$ describes the shape of the dose-response function and $e(e, s, a)$ describes risk variation with sex, time, or other factors. In addition to the simple linear dose response ($\rho(d) = \beta d$), we have considered various dose response models in these analyses, including

$$\begin{aligned} \rho(d) &= \beta d + \gamma d^2 && \text{Linear-quadratic} \\ \rho(d) &= \gamma d^2 && \text{Quadratic} \\ \rho(d) &= \begin{cases} \beta(d - d_i) & d > d_i \\ 0 & d \leq d_i \end{cases} && \text{Linear threshold} \\ \rho(d) &= \delta_j \quad d_{j-1} \leq d < d_j && \text{“Nonparametric”} \end{aligned}$$

The dose-response parameters are not constrained to be positive. The primary test for non-linearity is based on comparison of linear and linear-quadratic dose-response models. In a linear-quadratic dose-response model, the ratio γ/β describes the curvature of the dose response (in radiation biology, the reciprocal of this is referred to as the crossover

TABLE 2
Observed and Expected Solid Cancer Deaths 1950–1997 by Dose Group

Dose	People	1950–1997			1991–1997		
		Deaths	Expected background	Fitted excess	Deaths	Expected background	Fitted excess
<0.005	37,458	3,833	3,844	0	742	718	0
0.005–0.1	31,650	3,277	3,221	44	581	596	12
0.1–0.2	5,732	668	622	39	137	109	10
0.2–0.5	6,332	763	678	97	133	118	24
0.5–1	3,299	438	335	109	75	62	28
1–2	1,613	274	157	103	68	31	27
2+	488	82	38	48	20	8	13
Total	86,572	9,335	8,895	440	1,756	1,642	114

dose). The “nonparametric” specification above is useful for qualitative assessment of the nature of the dose response. To minimize the effect of arbitrary choice of dose categories, our implementation of this is to use the large number of dose categories in the analysis table and then smooth the resulting parameter estimates δ_j , which are individually quite imprecise due to the narrow width of dose categories. The smoothing method is a locally weighted linear regression described in ref. (5), with weights involving the standard errors of the estimates δ_j .

Effect modification is generally described using multiplicative models such as

$$\varepsilon(e, s, a) = \omega \exp\{\theta e + \gamma \log(a)\},$$

which we note applies equally to all dose levels. As a convention, of no real consequence, we parameterize the effect modification model so that $\rho(d)$ corresponds to the dose response, averaged over sex, for $e = 30$, $a = 70$.

Sex-specific parametric models for the background rates $\lambda_0(\cdot)$ are used in most analyses. For each sex, the logarithms of these include a city effect, piecewise quadratic functions of log age joining smoothly at ages 40 and 70, and piecewise quadratic functions of birth year joining smoothly at 1915 (age at exposure 30) and 1895 (age at exposure 50). A smooth piecewise quadratic function of x with join points at x_1 and x_2 can be written as $\beta_0 + \beta_1 x + \beta_2 x^2 + \beta_3 \max(x - x_1, 0)^2 + \beta_4 \max(x - x_2, 0)^2$. As noted later in the report, there are indications of time-dependent selection effects on noncancer disease baseline death rates. That is, early in the follow-up noncancer disease death rates at zero dose for proximal survivors are lower than those for distal survivors. For some analyses, we make use of an extended baseline risk model of the form

$$\lambda_0(c, s, a, b, I_{\text{prox}}) = \lambda_0(c, s, a, b)[1 + \psi I_{\text{prox}} e^{\phi(\text{year} - y_0)}],$$

where I_{prox} is an indicator of proximal exposure, the parameter β is an estimate of the proximal-distal baseline rate difference at the start of follow-up, and ϕ describes how the selection effect changes over time. This model can also be extended to allow for the possibility of a residual difference between the proximal and distal baseline rates by the inclusion of an additional multiplicative term of the form $e^{\delta I_{\text{prox}}}$. One limitation of this approach to describing selection effects is its complete reliance on proximal-distal distinctions for modeling selection effects, which will not completely eliminate bias due to distance-dependent selection effects among proximal survivors.

To a limited extent, the site-specific analyses in section 7 were carried out using the joint analysis methods developed in ref. (17). These joint analyses allow for simultaneous estimation of the effect for a specific site using an organ dose appropriate for that site and the risk for all other sites together using colon dose.

Estimates of the expected number of background deaths, such as those given in Table 2 (*expected background*), were computed by summing estimates of the number of background deaths over cells in the analysis data set. These cell-specific estimates were computed as the number of person-years in the cell times the product of the values of the background

rate estimate for that cell. The background model is fitted together with the part of the model representing the excess, using all the data. That is, parameter estimates for the background model are not based solely on a fit to the unexposed portion of the cohort. Estimates of the *fitted excess* in a cell are computed as the number of person-years times the fitted excess rate for that cell. In an ERR model, the fitted excess rate is defined as $\lambda_0(a, b, c, s) \cdot \text{ERR}(d, e, s, a)$, while for an EAR model the fitted excess rate is simply $\text{EAR}(d, e, s, a)$. The fitted excess consists of deaths that, in the absence of exposure, would not have occurred by the end of follow-up and also deaths hastened by the radiation exposure.

Lifetime risks were computed using the methods developed for recent UNSCEAR reports (18, 19). The basic methods have been discussed by Thomas *et al.* (20). The quantity used here has been called the risk of induced excess death or REID. It is computed as the integral over age of the difference between the rates for exposed and unexposed individuals (excess rate) weighted by the survival probability for an exposed individual.

Calculation of the coefficient of variation of lifetime risk estimates was done by propagating the statistical error of parameter estimates in the ERR model as follows. Following the notation above, the REID estimate for age-at-exposure e can be expressed as

$$\text{REID}(e; \hat{\beta}, \hat{\theta}, \hat{\alpha}, \hat{\omega}) = \hat{\beta} \hat{\theta} \exp(\hat{\alpha} e) g(e; \hat{\omega}),$$

where $g(e; \hat{\omega})$ is an integral over attained age that is numerically evaluated in the life-table calculations. The logarithm of the REID is then approximated as a linear function of the parameter estimates, where the derivative of $g(e; \hat{\omega})$ with respect to $\hat{\omega}$ was calculated numerically. This linear approximation, along with the covariance matrix of the parameter estimates, provides a variance estimate for the REID. This is of the same order of approximation as the covariance matrix of the parameter estimates themselves, arrived at by similar linear approximations. This is an instance of the standard “delta method”, or “method of statistical differentials” (21).

3. SOLID CANCER

3.1 Overview

Solid Cancer Data

Table 2 summarizes the distribution of cancer deaths by radiation dose category for the full follow-up period and for the 7 years since the last general report. The expected numbers of background cases are based on an ERR model with a linear dose response fitted to all of the data. This model includes attained age, age at exposure, and sex effects in the ERR with background rates modeled as described in the Materials and Methods section. The ERR

TABLE 3
Cancer Deaths and Excess Rates by Calendar Period and Age at Exposure

Age at exposure	1950–1967		1968–1977		1978–1987		1988–1997	
<20	45 ^a	9 ^b	189	22	434	49	954	93
	600,571 ^c	1.5 ^d	339,417	6.5	330,099	14.9	314,172	30.0
20–40	457	28	632	35	1,055	51	1,219	57
	383,845	7.4	203,469	17.0	177,961	28.6	135,960	41.8
>40	2,055	42	1,192	27	769	19	334	6
	379,769	11.1	121,534	22.5	58,389	31.8	16,860	38.4

^a Observed deaths.

^b Estimated radiation-associated deaths.

^c Person-years.

^d Estimated excess rate (deaths per 10,000 PY).

parameter estimates used are given in Section 3.3. While Table 2 provides a useful summary of the data, detailed inferences about the dose response should be based on the more incisive statistical methods employed later in the paper.

We estimate that there were about 440 radiation-related cancer deaths for the cohort between 1950 and the end of 1997. As noted in previous reports, the LSS cohort is likely to include only about half of the proximal survivors, and doses have been assigned to about 80% of these. Thus we estimate that there may have been about $440/(0.50 \times 0.80) = 1100$ radiation-related solid cancer deaths during the follow-up period among the several hundred thousand people considered as A-bomb survivors.

About 25% of radiation-related cancers have occurred during the last 7 years of follow-up, which comprises only 13% of the follow-up, indicating persistence of the excess risk. Table 3 presents estimates of the number of radiation-associated cancer deaths by age at exposure and time periods. For those exposed prior to age 20, the estimated number of radiation-associated deaths has roughly doubled in each of the last three 10-year periods and, for those who were 20 to 39 years old at exposure, the estimates have

increased steadily with time. The decrease in the number of radiation-associated deaths for the oldest group in this table reflects the rapidly decreasing number of people in this group who are still alive. The left panel of Fig. 1, which portrays the estimated excess cancer rates from Table 3, indicates that the excess rates increase with time within each age-at-exposure group. The right panel illustrates the changes, over time, in the ratio of the excess rate to estimated background rates within age-at-exposure groups. The decline in the age-at-exposure-specific ratios, which is most apparent for the two youngest groups, indicates that the increase with age in excess rates is less rapid than the normal increase in cancer rates with age.

Dose Response

Figure 2 summarizes the sex-averaged dose response for solid cancers using (a) ERR estimates for a large number of specific dose categories, (b) a smoothed curve (with indication of its uncertainty) based on the category-specific estimates without assumptions about the shape of the dose-response function, and (c) a linear dose response fitted to the full data set. The estimates in this figure were made

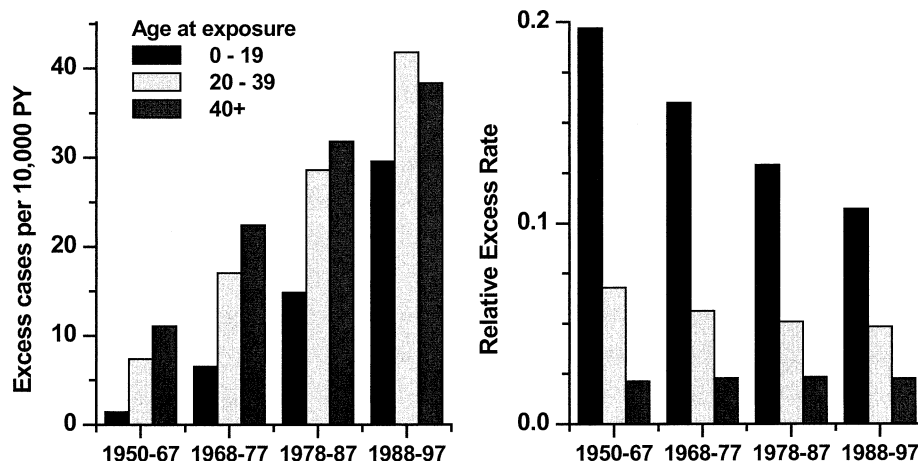


FIG. 1. Excess cancer rates by calendar periods and age-at-exposure categories: absolute and relative to background rates.

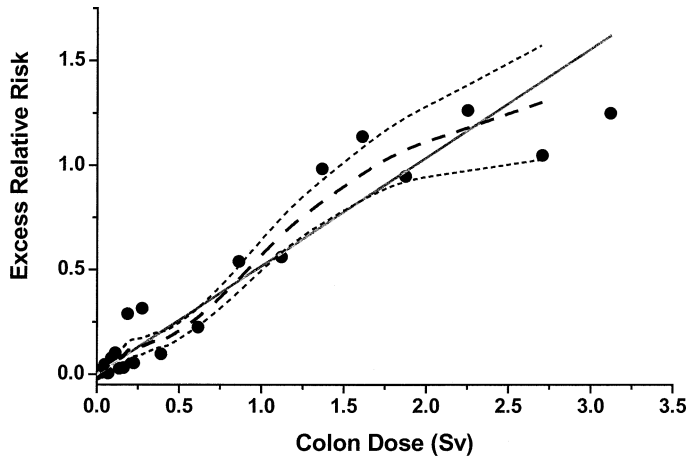


FIG. 2. Solid cancer dose-response function averaged over sex for attained age 70 after exposure at age 30. The solid straight line is the linear slope estimate, the points are dose category-specific ERR estimates, the dashed curve is a smoothed estimate derived from the points. The dotted curves indicate upper and lower one-standard-error bounds on the smoothed estimate.

with allowance for sex, attained-age, and age-at-exposure effects. Here, and throughout the paper unless otherwise indicated, ERRs are sex-averaged estimates at age 70 for a person exposed at age 30. There is little evidence against a simple linear dose response, with the only apparent curvature being a flattening for those with dose estimates above 2 Sv that is not statistically significant ($P > 0.5$). The ERR per Sv estimate is 0.47 ± 0.06 . Although variation in the ERR with sex, age at exposure, attained age and other factors precludes this estimate being interpreted as *the* LSS radiation risk estimate, it provides a useful benchmark for describing radiation effects on LSS solid cancer risks.

Direct assessment of the radiation-associated solid cancer risks at low doses in the LSS indicates a statistically significant increase with dose when analysis is restricted to

survivors with dose estimates less than about 0.12 Sv. The ERR per Sv estimate over this range is 0.74 (90% CI 0.1; 1.5). There is no indication that the slope of this dose-response curve over this low-dose range differs significantly from that for the full range ($P > 0.5$) and no evidence for a threshold.

Age-Declining ERR and Lifetime Risks

Since it remains difficult to distinguish between attained age and age-at-exposure effects on the ERR, we have chosen to emphasize a descriptive model that allows the ERR to vary with both attained age and age at exposure. However, we also give results for an attained-age-constant ERR model under which, as in previous reports, the ERR is taken to vary only with age at exposure. The left panel of Fig. 3 contrasts fitted, sex-averaged ERR per Sv estimates obtained from age-constant and age-varying ERR models for several age-at-exposure groups. The right panel presents a description in terms of the fitted EAR models. Formal descriptions of these models and the underlying parameter estimates are presented in Section 3.3.

The ERR estimates in the left panel exhibit a decline with attained age, especially for those exposed in childhood, while the data summarized in the right panel of Fig. 3 indicate that radiation-associated rates of excess solid cancer are increasing with time within age-at-exposure groups.

Age-varying ERR estimates are more difficult to describe and explain than are those in which the excess risk is constant with attained age. For this reason, lifetime risk estimates, which have long been an important part of UNSCEAR (18) or BEIR (22) reports, are increasingly important summaries of radiation-associated excess risks in the LSS cohort. These are presented in Section 3.4 along with an assessment of how results differ for age-declining and age-constant ERR models. For those exposed as adults, life-

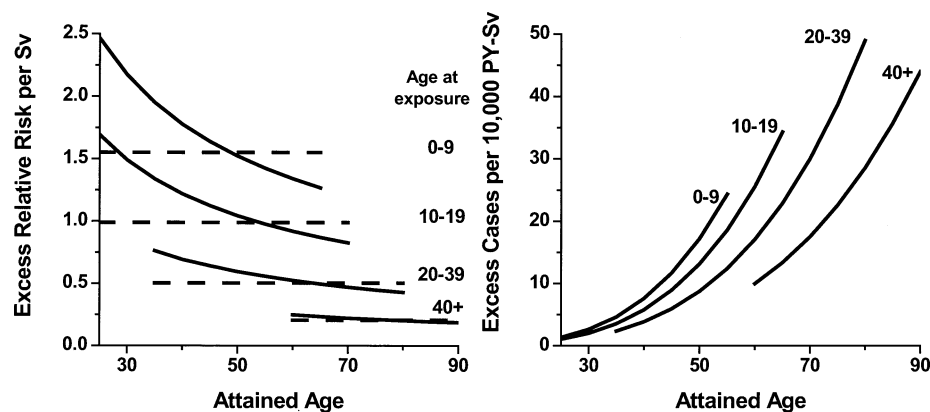


FIG. 3. Primary descriptions of the excess risks of solid cancer. The left panel presents fitted sex-averaged ERR estimates using both attained-age-declining (dark solid line) and attained-age-constant (dashed lines) forms, for age-at-exposure groups 0–9, 10–19, 20–39 and 40+. ERR estimates for women are about 25% greater and ERR estimates for men are 25% lower than the values shown. The right panel presents fitted EAR estimates for the same dose groups. There is no evidence of significant sex differences in the fitted EAR. The details of these models are given in Section 3.3.

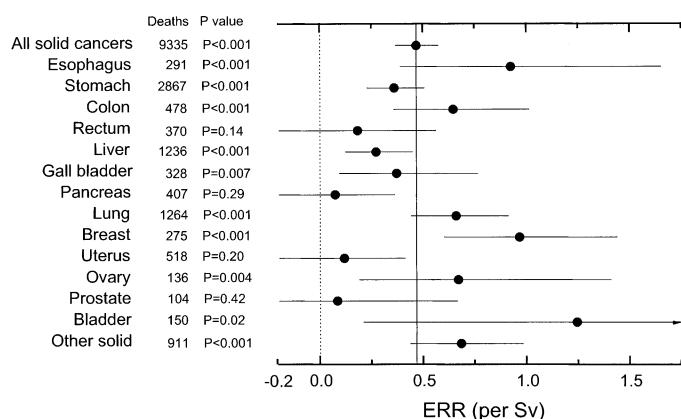


FIG. 4. Estimates of the site-specific solid cancer ERR with 90% confidence intervals and one-sided P values for testing the hypothesis of no dose response. Except for sex-specific cancers (breast, ovary, uterus and prostate), the estimates are averaged over sex. All estimates and P values are based on a model in which the age-at-exposure and attained-age effects were fixed at the estimates for all solid cancers as a group. The light dotted vertical line at 0 corresponds to no excess risk, while the dark solid vertical line indicates the sex-averaged risk for all solid cancers.

time risk estimates are essentially identical under these two models. For those exposed as children, lifetime risk estimates under the age-declining ERR model are 15–20% smaller than under the age-constant ERR model. This does not, however, represent a departure from previous conclusions since the same contrast was seen in the previous report (1) when considering various projections beyond follow-up for those exposed as children.

Site-Specific Cancer Risks

There is interest in comparing radiation risks for cancers of specific types. Figure 4 presents ERR estimates and 90% confidence intervals for solid cancers as a group, for 13 types of cancer, and for a group that includes all other solid cancer deaths. The estimates are standardized to age 70 after exposure at age 30 and averaged, where appropriate, over sex. For this plot, age-at-exposure and attained-age effects were taken as the same for all sites. As we have discussed elsewhere (1, 17), care should be taken to avoid over-interpretation of differences in site-specific ERRs since the variability in this plot is not markedly greater than one would expect if the ERRs were equal to that for all solid cancers. In contrast to the previous report (1, 17), where the plot was very similar, the variation is statistically significant (χ^2 28.8 on 13 df, $P = 0.01$). This χ^2 statistic is reduced by 3.8 but remains statistically significant if, as in the previous report, separate age-at-exposure effects are allowed for lung and breast cancer. The largest contribution to the χ^2 is from uterus (6.0), followed by pancreas (4.6).

In this report we also investigate how the radiation dose response varies with attained age, age at exposure, and sex, for five common types of solid cancer (stomach, colon, liver, lung and female breast) and all other solid cancers as a

group. These analyses indicate that, with the possible exception of colon cancer, for which the ERR decreases especially rapidly with attained age, the ERR age-time patterns are similar. With regard to the EAR, statistically significant departures from the solid cancer temporal patterns are seen only for breast cancer, which has a larger age-at-exposure effect, and lung cancer, for which excess rates increase more rapidly with attained age.

Our consideration of site-specific risks highlights difficulties in generalizing radiation age-at-exposure effects (Sections 3.5 and 3.6). These difficulties arise from confounding of those effects with birth cohort trends in background rates. This confounding is particularly acute in the LSS due to the equivalence of birth cohort and age at exposure. Traditionally, age-at-exposure effects on the ERR are emphasized more than those on the EAR, but these ERR variations are generalizable radiation effects only if factors responsible for the birth cohort trends act multiplicatively with radiation, that is, if these factors modify absolute radiation risks in the same manner as they modify background risks. Often, however, it appears that these factors act rather more additively with radiation, as has been shown for smoking and lung cancer in the LSS (23) and appears likely to be the case for factors causing trends in stomach cancer rates. In such cases it is age-at-exposure effects in the EAR that are more generalizable.

We now turn from this overview to detailed treatment, in Sections 3.2–3.6, of specific topics regarding cancer mortality

3.2 Solid Cancer Dose Response

Figure 2, given earlier, included a nonparametric description of the solid cancer dose response. To minimize the effect of the choice of dose categories for this type of nonparametric description, we used a large number of narrow categories to obtain the points and smoothed the results to obtain the dashed curve. The dotted curves indicate one standard error bounds for the smoothed curve. The linear regression on the full dose range, indicated by the solid line differs little from that on more restricted dose ranges such as 0–2 Sv.

There is no indication of upward curvature in dose, and the smoothed nonparametric estimate even at doses as low as 0.05 Sv coincides with the linear regression on the full dose range. We want to emphasize that the LSS is not, as commonly characterized, a “high-dose” study, although it involves high dose rates. In fact, among survivors with dose estimates of 5 mSv or more 76% have doses less than 200 mSv, and 64% less than 100 mSv. While it is true in principle that observations at high doses could dominate linear regression on the full dose range, because of the extent of the linearity, they do not for these data. Table 4 presents ERR/Sv estimates and P values for testing the hypothesis of no dose effect computed using data in the indicated dose ranges. In every case the full dose range was

TABLE 4
Excess Relative Risk Estimates for Selected
Dose Ranges

Dose	ERR/Sv (SE) ^a	<i>P</i> value ^b
0–0.05	0.93 (0.85)	0.15
0–0.1	0.64 (0.55)	0.30
0–0.125	0.74 (0.38)	0.025
0–0.15	0.56 (0.32)	0.045
0–0.2	0.76 (0.29)	0.003
0–0.5	0.44 (0.12)	<0.001
0–1	0.47 (0.10)	<0.001
0–2	0.54 (0.07)	<0.001
0–4	0.47 (0.05)	<0.001

^a Sex-averaged estimates at age 70 after exposure at age 30.

^b One-sided *P* value for a test of the hypothesis that the slope is 0.

used to estimate the modifying effects of sex, age at exposure, and attained age. As indicated in Table 4, the estimated dose–response slope (ERR/Sv) is quite constant for dose ranges that include 0 to 0.5 Sv while the estimates are slightly larger for more restrictive dose ranges. The primary impact of restricting the dose range is to increase the standard error of the slope estimate.

Although we believe that too much emphasis is placed on the minimum dose at which a significant response is seen, we note that the one-sided *P* values for evidence of radiation risk on the dose ranges 0–0.10 and 0–0.125 Sv, using regression linear in dose, are respectively 0.30 and 0.025. Note that the latter of these *P* values means that, when restricting the dose range to 0–0.125 Sv, the 95% confidence interval for the ERR/Sv, namely 0/Sv to 1.5/Sv, has a lower limit of zero. Thus, to emphasize that 0.125 Sv is the lowest dose below which a statistically significant risk is found focuses on the *smallest* plausible risk in that dose range. This seems inappropriate for radiation carcinogenesis, where mechanisms are relatively clear and effects are seen at moderate doses.

In ref. (1) we found a statistically significant risk on the 0–0.05-Sv dose range. We noted that the ERR/Sv in the 0.005–0.02 and 0.02–0.05-Sv dose categories were both inordinately large and suggested that this was likely due to small biases in the recording of causes of death. Whatever its causes, this anomaly has largely disappeared with further accumulation of data, and as shown in Table 4, the dose response over the range 0–0.05 Sv is no longer statistically significant. The statistical significance on the range 0–0.125 Sv is not overly influenced by risks in very low dose categories. In particular, the *P* value for that range is unchanged by omission of data on the 0–0.02-Sv range, even though the ERR/Sv estimate for this range is 1.4.

In a recent discussion of low-dose risks in the LSS, Pierce and Preston (5) emphasized analyses of cancer incidence data restricted to those within 3,000 m of the bombs. This restriction can be useful when focusing on estimation of small risks at low doses, since there may be differences between the zero-dose proximal and distal sur-

vivors due to factors other than radiation exposure. We do not pursue that matter here except to note that the effect of omitting survivors beyond 3,000 m is essentially as reported in ref. (5)—the zero ERR baseline in Fig. 2 is moved down by approximately 0.05, and the standard errors leading to the dashed curves are slightly increased.

Although for various reasons city comparisons should await the dosimetry revision, there is no statistically significant city difference in either the ERR or EAR with the present data. There are about 650 Nagasaki factory workers with difficult shielding situations having significantly lower risk, and this group is being given special attention in the dosimetry revision. Setting these aside, the *P* values for a city difference are greater than 0.50 for both the ERR and EAR, and even when the factory workers are included, the city difference is not statistically significant.

3.3 Age–Time Patterns of Excess Solid Cancer Risk

Figure 5 displays the temporal pattern of solid cancer ERR and EAR estimates over the follow-up period for four age-at-exposure groups, 0–9, 10–19, 20–39 and 40+. The curves are estimated separately for each age-at-exposure group, and the points correspond to risks in 10-year follow-up intervals. The ERR estimates are averaged over sex, with the ERR for women being about 65% larger than that for men, but otherwise having similar patterns. This difference largely offsets the inverse sex ratio in background rates so that sex differences in the EAR are negligible. The agreement between the imprecisely estimated points and the fitted curves is reasonable. A large ERR estimate for the 0–9 group prior to age 30 is not shown.

It is difficult in any cohort study to distinguish between variation in risks with age at exposure and variation with attained age. That this is possible in the LSS is due to the large study population, the lengthy follow-up, and the broad dose range. Although variation by tumor type in the temporal patterns of the ERR complicates interpretation of the patterns seen for all solid cancers as a group, we feel that these summaries provide useful insights into the nature of the radiation-related excess mortality risks in the LSS. The nature of the temporal patterns for a number of major cancer types is considered later. In terms of the general description provided by Fig. 5, there is clearly variation in the ERR with age at exposure, but the evidence for a decline with attained age is weaker. Significance tests for this based on simpler statistical models are considered below. The magnitude of the variation of the EAR with age at exposure is somewhat smaller than that for the ERR, whereas the increase with attained age in the EAR is very strong in spite of the decrease of the ERR.

The plots in Fig. 5 require a large number of parameters, and there is need for more parsimonious descriptions. In our previous reports, the primary description was in terms of age-constant ERR depending on age at exposure. This is useful in its simplicity, and may be more accurate, even

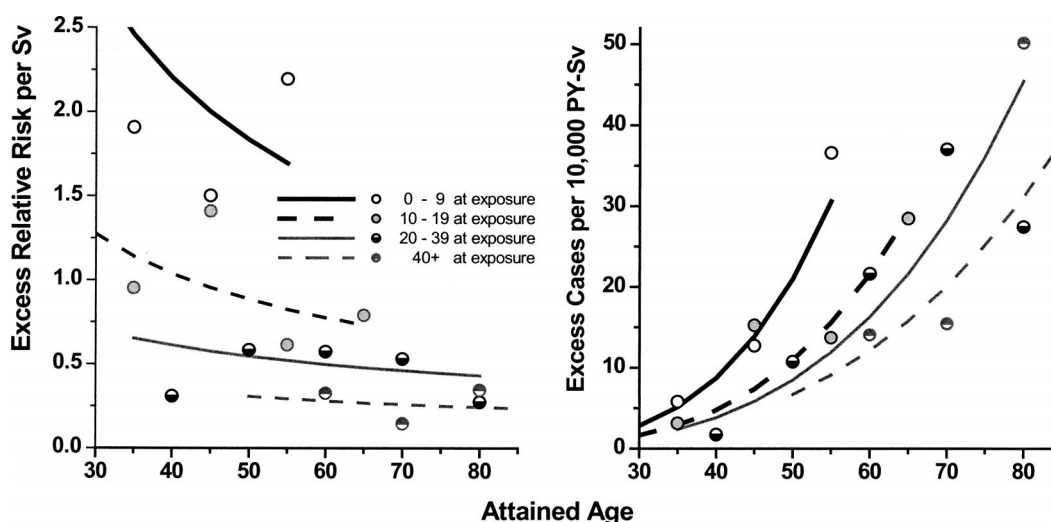


FIG. 5. Age-time patterns for the solid cancer ERR and EAR for age-at-exposure groups 0–9, 10–19, 20–39 and 40 or more. The curves are power functions of attained age fitted separately for each age-at-exposure category. The points are estimated values for decades of attained age within each age at exposure group.

for those exposed as children, than suggested by Fig. 5, since it is particularly difficult to distinguish between age-at-exposure and attained-age effects for those exposed early in life. This description led, however, to the consideration of several methods to project future risks for those exposed as children, for whom the ERR is likely to decrease with age. An alternative and more unified description, emphasized in this report, can be based on a model that allows the ERR to vary with age at exposure while also varying with attained age. Figure 3, given earlier, contrasts attained-age-constant and attained-age-varying descriptions of the solid cancer ERR.

The equations for the sex-averaged descriptions in the left panel of Fig. 3 are

$$\text{ERR} = 0.47d \exp\{-0.038(\text{agex} - 30) - 0.70 \log(\text{age}/70)\} \quad \text{and}$$

$$\text{ERR} = 0.50d\{\exp[-0.045(\text{agex} - 30)]\}$$

for weighted dose d in Sv. In such formulas the coding of agex and age is just a convention so that the coefficient of dose will mean the ERR/Sv at age 70 for those exposed at age 30, and the coefficients of agex and age are unaffected by this choice. Table 5 presents parameter estimates with

90% confidence intervals. The table includes both the sex-averaged and sex-specific dose–effect estimates.

Clearly the relative risks are greater for women than for men ($P < 0.003$), but this largely serves to offset a reciprocal ratio in background rates, and there is little sex difference in the EAR. There is strong evidence for a decrease in the ERR with increasing age at exposure ($P < 0.001$). There is also modest evidence (one-sided $P = 0.07$) that the ERR, adjusted for age at exposure, declines with increasing attained age. The decline in the ERR with attained age is most clearly seen in the two youngest age-at-exposure groups. The point estimates of the attained age effect are -0.80 for people exposed under age 20 and -0.53 for people who were over 20 years old when exposed. These estimates do not differ significantly ($P > 0.5$).

While direct statistical evidence is modest for an attained-age effect on the solid cancer ERR, we feel that there are good reasons to consider it in descriptions of solid cancer risks. A decrease for those exposed as children has been emphasized in previous reports as a likely and important departure from age-constant ERR models. As seen in the left panel of Fig. 3, the more unified model used here captures that variation while introducing only modest and largely inconsequential age variation for those exposed as

TABLE 5
Solid Cancer Excess Relative Risk Model Parameter Estimates

Model	Dose effect (ERR/Sv) ^a			Age at exposure (percentage change per decade increase)	Attained age [log(age/70)]
	Male	Female	Sex-averaged		
Attained age and age at exposure	0.35 (0.24; 0.46) ^b	0.59 (0.45; 0.74)	0.47 (0.37; 0.57)	–31% (–42%; –20%)	–0.70 (–1.4; 0.08)
Age at exposure only	0.37 (0.26; 0.49)	0.63 (0.49; 0.79)	0.50 (0.40; 0.60)	–36% (–45%; –27%)	

^a At age 70 after exposure at age 30.

^b Numbers in parentheses are 90% of confidence interval.

TABLE 6
Solid Cancer Excess Absolute Rate Model Parameter Estimates

Model	Dose effect (Excess cases per 10,000 PY-Sv) ^a			Age at exposure (percentage change per decade increase)	Attained age [log(age/70)]
	Male	Female	Sex-averaged		
Attained age and age at exposure	29 (30; 39) ^b	30 (24; 37)	30 (24; 36)	−23% (−34%; −12%)	3.6 (3.0; 4.4)

^a At age 70 after exposure at age 30.

^b Numbers in parentheses are 90% of confidence interval.

adults. Further, as will be discussed in the next LSS solid cancer incidence report, there is strong evidence for cancer incidence of a general decrease in the ERR with increasing attained age, as well as with increasing age at exposure. In addition, theoretical stochastic analysis (24–26) of accumulation of mutations causing cancer, and mutagenic effects of radiation, indicates why the ERR should be expected to decline roughly as $1/\text{age}$.

As illustrated in the right panel of Fig. 3, the attained-age-dependent EAR provides a useful complement to ERR-based descriptions of LSS excess cancer risks. The curves in the right panel in Fig. 3 displays the primary EAR model developed for the current solid cancer data. The equation for the EAR description shown in the figure is

$$\text{EAR} = 30 d \exp \{ -0.027(\text{agex} - 30) + 3.7 \log(\text{age}/70) \}$$

with units of excess cases per 10,000 PY. The log-log slope in age of 3.7 is somewhat less than the corresponding age increase in background rates, which is the reason that the ERR decreases with age. Table 6 presents the parameter estimates and confidence intervals for this EAR model.

Both the decrease in age-specific excess rates with increasing age at exposure and the increase in the excess rates with attained age are significant ($P < 0.001$). There is no indication of a significant sex difference in EAR ($P > 0.5$). There is no statistically significant attained-age by age-at-exposure interaction ($P = 0.5$), or significant sex differences in either the age-at-exposure effect ($P > 0.5$) or attained-age trend ($P = 0.2$). This simple EAR model describes the data only slightly less accurately than the primary ERR models, with the deviance difference for these non-nested models with comparable numbers of parameters being 5.5.

Age at exposure has an important and highly significant effect on the LSS solid cancer mortality ERR and EAR. However, confounding between birth cohort trends in background rates and age-at-exposure effects makes it difficult to interpret this as a generalizable radiation effect, especially since birth cohort trends in LSS background rates over the last 50 years are different from those in other countries or what would be seen for different periods in Japanese populations. This issue is best considered in the context of site-specific analyses, which are presented in section 3.5.

Thus there are substantial uncertainties regarding both generalizable age-at-exposure effects and variations of ex-

cess risks with attained age. The continued follow-up of those exposed as children—adding further “points” for the top curves in Fig. 5—will clarify the distinction between age-at-exposure and age effects. However, additional follow-up will do little to resolve uncertainties regarding the interpretation of age-at-exposure effects noted above and discussed again in Section 3.6.

3.4 Lifetime Risks

The use of age-declining ERR descriptions of the excess risk raises new issues regarding simplified description of the radiation risk. It is no longer adequate to say that for a given age at exposure the solid cancer risk is increased by a certain percentage per sievert for all remaining lifetime. Because of this, lifetime risk calculations are increasingly important summaries of varying age-specific risks. The term lifetime risk as used here [the REID defined in Section 2.2 and in ref. (20)] refers to the chance of a radiation-associated death after exposure, including cancer deaths that would have occurred anyway but were hastened by exposure. This is necessarily an incomplete summary, since it does not provide information on when radiation-associated deaths occur. As in refs. (1, 2), to deal with this deficiency, we supplement the lifetime risk estimates with estimates of the years of life lost per radiation-associated death, which is the expected life shortening divided by the lifetime risk and depends little on dose.

As in LSS Report 12 (1, 2), we estimate lifetime risks using lifetable calculations based on background cancer rates and all-cause death rates for the LSS cohort. Because of the marked changes in these age-specific rates over the follow-up period, these LSS-based lifetime risk estimates differ from what would be estimated based on rates for another population or even for the current Japanese population. By restricting these inferences to the LSS cohort, we avoid difficulties in generalizing LSS radiation risk estimates for use with a different population or in a different time period.

Table 7 presents estimates by age at exposure for a dose of 100 mSv, which is representative of the typical doses received by cohort members and generally more relevant to the concerns of radiation protection than are the doses of 1 Sv used in many presentations of lifetime risks. Furthermore, extrapolation from 1 Sv to considerably lower doses tends to underestimate the low-dose lifetime risk, since even for a linear dose response, lifetime risks are not

TABLE 7
Estimated Lifetime Risk of Radiation-Associated
Solid Cancer Deaths in the LSS after
Exposure to 0.1 Sv

Age at exposure	Sex	Lifetime risk (%)	Years of life lost per excess death	Background risk (%)
10	M	2.1	13.0	30
	F	2.2	13.3	20
30	M	0.9	12.7	25
	F	1.1	14.4	19
50	M	0.3	10.2	20
	F	0.4	11.2	16

linear in dose. These estimates are based on the primary ERR description with age-at-exposure and attained-age effects presented in the previous section. Although several methods were used in refs. (1, 2) to project beyond follow-up the ERR for those exposed as children, the need for this is less pressing here due to the primary model allowing for age-declining ERR. Some comparisons relevant to this are given below.

Lifetime risk estimates were also computed using the pri-

mary EAR description given in the previous section. They are almost identical to the ERR-based estimates for people exposed at ages of 30 or more, while for those exposed as children the EAR-based lifetime risks are about 25% lower for men and 25% higher for women than the ERR-based estimates in Table 7.

Figure 6 presents estimates of sex- and age-at-exposure-specific lifetime risk and years of life lost per excess death, based on several models. The age-constant ERR model leads to the largest lifetime risk estimates. As noted above, under the EAR model, estimated lifetime risks after childhood exposures are larger for women and smaller for men than estimates based on the age-declining ERR model. Estimates of life lost per excess death are largest for models that predict lower lifetime risks. For the models considered here, life lost per excess death is fairly constant, averaging about 12 years, for exposures prior to age 40, but declines markedly for exposures that occur later in life.

By propagating to the lifetime risk calculations the statistical error in the parameter estimates for the ERR model, we have estimated the coefficient of variation of sex- and age-at-exposure-specific lifetime risk estimates. For either sex, this coefficient of variation has a minimum of about

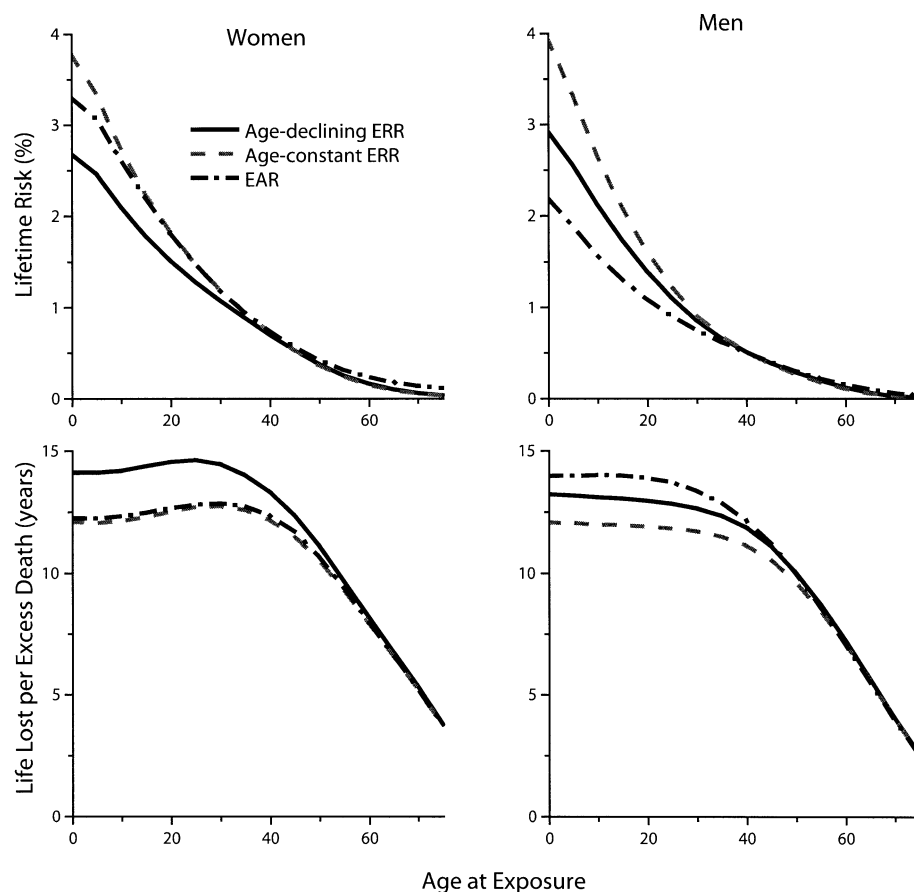


FIG. 6. Estimates of LSS lifetime solid cancer mortality risk and years of life lost per excess death, by age at exposure and sex and for a 100-mSv exposure. Estimates are based on age-declining (dark solid lines) and age-constant (light dashed lines) ERR models and an EAR model (dark dashed lines). The parameter estimates for these models are given in Tables 5 and 6 and the estimated excess risks were plotted in Fig. 3.

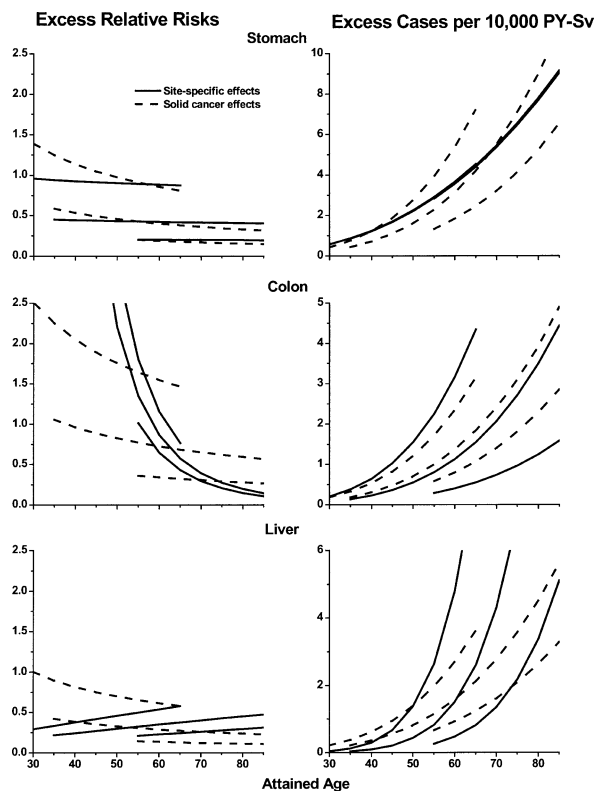


FIG. 7. Site-specific age-time patterns in the radiation-associated risks for stomach, colon and liver cancer. The dark curves are fitted age-time patterns in the ERR (left side) and EAR (right side). The light dashed curves are the patterns obtained when the age and age-at-exposure effects are constrained to equal that for all other solid cancers. The curves are sex-averaged estimates of the risk at 1 Sv for people exposed at age 10, 30 and 50 with attained ages corresponding to the follow-up period.

20% for ages at exposure near 35 and is about 40% for those exposed early or late in life. Although there are other uncertainties related to the choice of a summary risk model, this assessment accounts for the choice between age-declining and age-constant ERR models since the statistical uncertainty of the age decline is represented in the calculations.

There are many additional uncertainties in making generalizations from the LSS, such as those associated with extrapolation to very low doses and dose rates, or whether ERR or EAR estimates should be used to “transport” risks for sites like stomach and lung cancer to populations in which the background rates are markedly different from those in the LSS. The latter issue is considered in UNSCEAR (18) and BEIR (23) reports.

3.5 Site-Specific Risks

In Fig. 4 we summarize the general level of the ERR for specific sites using the same age-time pattern for all sites. In this section we compare the age-time patterns of risk for several major cancer sites to those for solid cancers in general allowing for site-specific levels of risk and sex effects. Comparisons are made for stomach, colon, liver, lung,

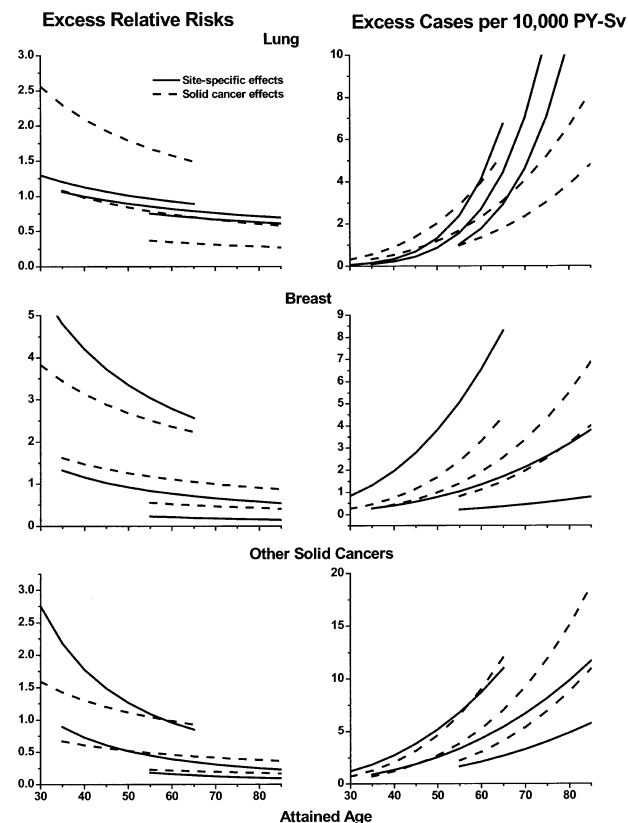


FIG. 8. Site-specific age-time patterns in the radiation-associated risks for lung, breast and all solid cancers other than stomach, colon, liver, lung and breast. The dark curves are fitted age-time patterns in the ERR (left side) and EAR (right side). The light dashed curves are the patterns obtained when the age and age-at-exposure effects are constrained to equal that for all other solid cancers. The curves are sex-averaged estimates of the risk at 1 Sv for people exposed at age 10, 30 and 50 with attained ages corresponding to the follow-up period.

breast and all other sites combined. The statistical models fitted for this purpose take the same mathematical form for the ERR and EAR, namely

$$\text{excess risk} = \beta_{\text{sex}} d \exp\{\theta \text{ agex} + \gamma \log(\text{age})\},$$

where *agex* is age at exposure. For the ERR the parameter γ represents what is generally a decline in the ERR with attained age. For the EAR, γ describes the strong increase of excess cancer rates with attained age, similar to but usually somewhat less rapid than the age increase in background rates. The parameter θ has a similar interpretation in both the ERR and EAR models, but with a distinction discussed below.

Each graph in Figs. 7 and 8 compares the age-time patterns for a specific site to that for all solid cancers as a group. Patterns are given for three ages at exposure (10, 30 and 50).

Stomach cancer. There were 2,867 stomach cancer deaths, with 1,685 among people with doses in excess of 5 mSv. About 100 of these are estimated to be related to atomic bomb radiation exposure. For the ERR analysis, the *P* value for joint departure of (θ, γ) from the estimates for

other solid cancer in general is >0.50 , with no notable difference for either parameter. For the EAR analysis, this P value is 0.21, with no significant difference for either parameter. It is notable, however, that in contrast to the ERR, the EAR age-at-exposure effect for stomach cancer is essentially nil and substantially less than that for all solid cancers. Since stomach cancer accounts for 30% of the solid cancer deaths, one should consider whether or not stomach cancer has an inordinate effect on the age-time patterns seen for all solid cancers. To examine this, we fit our primary risk model omitting stomach cancer and found that the resulting parameter estimates were similar to those from the all-solid-cancer fit.

Colon cancer. There were 478 colon cancer deaths, with 272 among people with doses in excess of 5 mSv. About 30 cases are estimated to be related to atomic bomb radiation exposure. For the ERR analysis, the P value for joint departure of (θ, γ) from the solid cancer estimates is 0.05, due almost entirely to the much more rapid decrease with age. Additional analyses indicate that this apparent rapid decrease derives entirely from the data for women. For the EAR analysis, this P value is 0.47, with no significant or notable difference in either parameter. Thus, although the ERR decreases rapidly with age, the age increase of the EAR is essentially the same as for all solid cancers, indicating that the peculiarity in the ERR derives from the rapid increase of the background rate (for females) rather than from the radiation effect.

Liver cancer. There were 1,236 liver cancer deaths, with 699 among people with doses in excess of 5 mSv. About 50 cases are estimated to be related to atomic bomb radiation exposure. In an ERR analysis, the P value for joint departure of (θ, γ) from the solid cancer estimates is 0.4, with no statistically significant difference for either parameter. In particular, although the ERR is estimated to increase moderately with age, the estimate is imprecise and not significantly different from the decrease for solid cancer ($P = 0.35$). Results from RERF's recent analysis of the LSS liver cancer incidence (27) suggested an unusual age-at-exposure dependence in the liver cancer ERR, with high risks for people exposed in their 20s but little excess risk for those exposed under age 10 or after age 45. There is no indication of this pattern in the mortality data, but this may, to some extent, be due to the poorer quality of death certificate diagnoses of liver cancer. For the EAR analysis, the joint departure P value is 0.12, with most of the difference due to the much more rapid increase with age, but this is only marginally significantly greater than for other solid cancer ($P = 0.05$).

Lung cancer. There were 1,264 lung cancer deaths, with 754 among people with doses in excess of 5 mSv. About 100 of these are estimated to be related to atomic bomb radiation exposure. For the ERR analysis, the P value for joint departure of (θ, γ) from the solid cancer estimates is 0.11, with most of the difference due to the small age-at-exposure effect. For the EAR analysis, this P value is

0.001, with most of the difference due to the much more rapid increase with age, which is significantly different from other solid cancer ($P = 0.003$). Note, however, that the age variation in the ERR is the same as for other solid cancers.

Breast cancer. There were 272 breast cancer deaths, with 176 among women with doses in excess of 5 mSv. About 40 of these are estimated to be related to atomic bomb radiation exposure. For the ERR analysis the P value for joint departure of (θ, γ) from the solid cancer estimates is 0.31, with no statistically significant difference for either parameter. Although the difference is not statistically significant ($P = 0.19$), the age-at-exposure effect is about twice that for all solid cancers. The EAR analyses indicate significant differences ($P < 0.001$) between the breast cancer age-time patterns and those for all solid cancer. Virtually all of the evidence for this difference arises from the large age-at-exposure effect for breast cancer ($P = 0.003$). The RERF cancer incidence data (3, 28, 29), with far more cases, may be more useful for characterization of radiation effects on breast cancer risks. However, in view of the increasing breast cancer incidence and changes in survival resulting from increased screening and improvements in therapy, it is also likely that the age-time patterns for mortality and incidence may differ for this site. Indeed, a recent analysis of the LSS breast cancer incidence data (28) suggests that age-at-exposure effects on the ERR may be less marked for incidence than for mortality.

Other solid cancers. For other cancers together there are 3,215 deaths, with 1,916 among people with dose estimates in excess of 5 mSv. About 120 of these are estimated to be related to atomic bomb radiation exposure. For the ERR analysis, the P value for joint departure of (θ, γ) from the estimates for solid cancer in general is 0.23, with no statistically significant difference for either parameter. For the EAR, this P value is 0.26. For neither the ERR nor the EAR is there any notable distinction from the remaining solid cancers.

Site-specific excess risk summary. Figure 4 contrasts site-specific ERR levels obtained under the assumption of common age-at-exposure and attained-age trends for all sites. Without such an assumption, comparison of the level of risk would depend on the age at exposure and attained age. The analyses of the major sites described in this section suggest that there is enough similarity between sites in the age-time patterns to make such comparisons useful. However, as indicated above, there are interesting and plausible differences in the site-specific temporal patterns that cannot be precisely estimated because of the small number of radiation-associated cases at any specific site.

3.6 Age-at-Exposure and Sex Effects

As indicated by the site-specific analyses above, age-at-exposure effects on the ERR and EAR scale are often quite different. This is a consequence of changes in age-specific

TABLE 8
Comparison of Baseline Rate Birth Cohort Effect
and Age-at-Exposure Effects on the Solid Cancer
ERR and EAR

	Birth cohort ^a baseline rate	Change per decade	
		Radiation effect ^b	
		ERR	EAR
All solid	-1%	-31%	-24%
Stomach	-25%	-29%	1%
Colon	23%	-25%	-50%
Liver	16%	-12%	-40%
Lung	30%	-6%	-20%
Breast	4%	-49%	-54%
Other	-3%	-35%	-30%

^a Change per decade increase in year of birth.

^b Change per decade decrease in at exposure.

baseline rates over time, that is birth cohort trends. If there were no birth cohort trends, then the age-at-exposure effects on the ERR and EAR would be the same. In fact, since age at exposure and birth cohort are equivalent in the LSS, if we let the σ be the coefficient of a log-linear birth cohort trend as a function of year of birth and let θ and η describe log-linear trends in the ERR and EAR with age at exposure, then, with some idealization, $\eta = \theta - \sigma$. Thus differences between the ERR and EAR age-at-exposure effects raise the issue of which is more appropriate for generalization to populations with different birth cohort trends in baseline rates.

Table 8 presents summary measures of the age-at-exposure effect estimates on both the ERR and EAR and birth cohort trends for the cancer sites considered in the previous section. For most of the sites considered, the birth cohort trends are fairly large and the ERR and EAR age-at-exposure effects differ. As suggested by the idealized relationship given in the previous paragraph, the EAR effect is approximately equal to the difference between the ERR and the birth cohort effects. (The relationship does not hold precisely because the radiation effect estimates are based on models including more general descriptions of baseline-rate birth cohort effects, and the values given in the table are not exactly the log-linear trend coefficients.)

Age-at-exposure trends in the ERR are often taken as generalizable radiation effects. This is a reasonable assumption only if the factors responsible for the birth cohort trends in the baseline rates act multiplicatively with radiation. That is, the factors affect baseline rates and absolute radiation effects (excess rates) in the same manner. Improvements in therapy, including early detection, would likely result in this. On the other hand, if the factors responsible for the birth cohort trends act additively with respect to radiation, then age-at-exposure effects in the EAR would be more generalizable. The LSS data indicate that radiation and smoking have largely additive effects on lung cancer risks (22); thus, to the extent that birth cohort trends

for lung cancer are due to increased smoking, the age-at-exposure effect on the EAR may be more generalizable.

While the issue of the generalizability of ERR or EAR age-at-exposure effect estimates is particularly important for site-specific analyses, the question is also of interest for all solid cancers as group. Because the very different birth cohort trends seen for different sites tend to average out when considering all solid cancers, the radiation age-at-exposure effect estimates from the ERR and EAR models are similar, suggesting that these estimates may be generally useful for solid cancer mortality. However, it should be noted that the uncertainties associated with use of these estimates is substantially greater than the purely statistical uncertainty in the estimates themselves.

It should also be borne in mind that age-at-exposure effects for cancer incidence can differ markedly from those for mortality, in part due to differences in birth cohort trends. For example, the breast cancer results in Table 8 suggest that age-specific mortality in the LSS has changed very little over the course of the study. However, it is well known that breast cancer incidence in Japan has increased dramatically over the past decades (30), suggesting that the relatively small changes in mortality reflect improvements in survival. This difference suggests that age-at-exposure effects for breast cancer mortality and incidence are likely to differ, even though what is a generalizable radiation effect probably should not. Contrasts between age-at-exposure effects for mortality and incidence data will be considered in more detail in a forthcoming paper on LSS cancer incidence.

Sex ratios in radiation risk are also of interest. For solid cancers as a group, it has long been reported that the estimated EAR/Sv depends little on sex despite the significant sex effect on the ERR, suggesting that the sex ratio in the ERR/Sv largely serves to offset the sex ratio in solid cancer background rates. A simple explanation for this is that radiation largely acts additively with factors causing the sex ratio in background rates. In the remainder of this section, we use the results for specific cancer sites to explore the evidence for this explanation.

Table 9 provides information on sex ratios in excess risks and background rates for all solid cancers and for the specific sites considered in this section. The *P* values are for testing that the sex ratio is unity. Sex ratios in background rates generally vary with age, and those given in the table are the ratios of the mean rates over age, weighting with solid cancer rates for the sexes together. Except for liver cancer, the interpretation made for solid cancers together holds up well for major sites. The sex ratios in the EAR are not significantly different from unity, and the ERR sex ratios are approximately the reciprocal of background rate ratios. For liver cancer, the sex ratio does not differ significantly from one for either the EAR or the ERR. One possibility is that factors affecting the sex ratio in liver cancer background rates may act more multiplicatively than additively with radiation. For example, viral hepatitis, which

TABLE 9
Sex Ratios in Radiation Risk and Background Rates

	ERR			Background M/F	EAR F/M
	Male	Female	F/M		
All solid	0.347	0.588	1.7 ($P = 0.01$)*	1.8	1.0 ($P > 0.5$)
Stomach	0.196	0.636	3.2 ($P = 0.01$)	2.3	1.6 ($P > 0.5$)
Lung	0.472	1.05	2.2 ($P = 0.02$)	2.4	0.80 ($P = 0.36$)
Colon	0.370	0.414	1.1 ($P > 0.5$)	1.3	0.71 ($P > 0.5$)
Liver	0.402	0.400	1.0 ($P > 0.5$)	2.1	0.36 ($P = 0.25$)
Other	0.351	0.326	0.93 ($P > 0.5$)	1.3	0.91 ($P > 0.5$)

* P value for the null hypothesis of no sex difference, i.e. $F/M = 1$.

is more prevalent among men, and may be related to radiation exposure in the LSS (31–34), could be relevant to the unusual pattern seen for liver cancer.

4. NONCANCER DISEASE RISKS

We focus on noncancer diseases other than those of the blood diseases since, as indicated in ref. (2) and discussed briefly at the end of this section, radiation effects on noncancer diseases of the blood and blood-forming organs appear to be much larger than those for other noncancer diseases. Table 10 provides an overview of the noncancer disease mortality data comparable to that for solid cancer given in Table 2. As noted in ref. (2) and discussed further in this report, there are strong indications of a “healthy survivor” selection effect on baseline rates for proximal survivors during the first two decades after the bombs. While a statistically significant dose response is apparent without allowance for the healthy survivor effect, ERR/Sv estimate 0.095 ($P < 0.001$), failure to allow for the selection reduces the magnitude of the linear risk estimate and increases the apparent curvature of the radiation effect. The expected numbers of deaths in Table 10 were computed using the full follow-up period with allowance for selection effects on baseline rates, as described in the Materials and Methods section and documented in Section 4.1.

After allowing for the selection effect, the estimated ERR per Sv is 0.14 ± 0.03 with no indication of significant non-

linearity ($P = 0.4$ for a quadratic departure from linearity). The current data provide reasonable direct evidence for risks at around 0.75 Sv, which was not apparent in earlier analyses (2). Despite somewhat stronger evidence for linearity, it is not possible to rule out a pure quadratic model or even a threshold as high as 0.55 Sv (90% upper confidence bound).

Our primary ERR model does not allow for variations in the ERR with age at exposure, attained age, and sex because these factors were not statistically significant effect modifiers. Although estimates of age-at-exposure and sex effects on the ERR are comparable to those for solid cancer, they are less precisely estimated due to the smaller noncancer ERR. In Section 4.2 we consider alternative risk models that allow for such variation. We also consider a simple EAR model that provides a fit of comparable quality. In Section 4.3 we compare LSS noncancer disease lifetime risk estimates under these various choices of descriptive models. Our results suggest that within the LSS cohort, the lifetime risk of death from a radiation-associated noncancer disease after childhood exposure to 1 Sv is about half of that seen for solid cancer, while lifetime risks for people exposed as adults are roughly comparable to the corresponding solid cancer risk estimate. Because of uncertainties about the shape of the dose response and how the excess noncancer disease risks vary with age and age at exposure, lifetime risk estimates are considerably more uncertain than those for solid cancer, especially when con-

TABLE 10
Observed and Expected Noncancer^a Deaths 1950–1997

Dose (Sv)	1950–1997			1991–1997		
	Deaths	Expected background	Fitted excess	Deaths	Expected background	Fitted excess
<0.005	13,832	13,954	0	2,060	2,080	0
0.005–0.1	11,633	11,442	17	1,689	1,689	7
0.1–0.2	2,163	2,235	17	332	329	7
0.2–0.5	2,423	2,347	47	390	343	16
0.5–1	1,161	1,075	61	186	161	16
1–2	506	467	68	78	74	14
2+	163	111	40	25	17	6
Total	31,881	31,631	250	4,760	4,694	66

^a Excluding 222 deaths attributed to diseases of the blood and blood-forming organs.

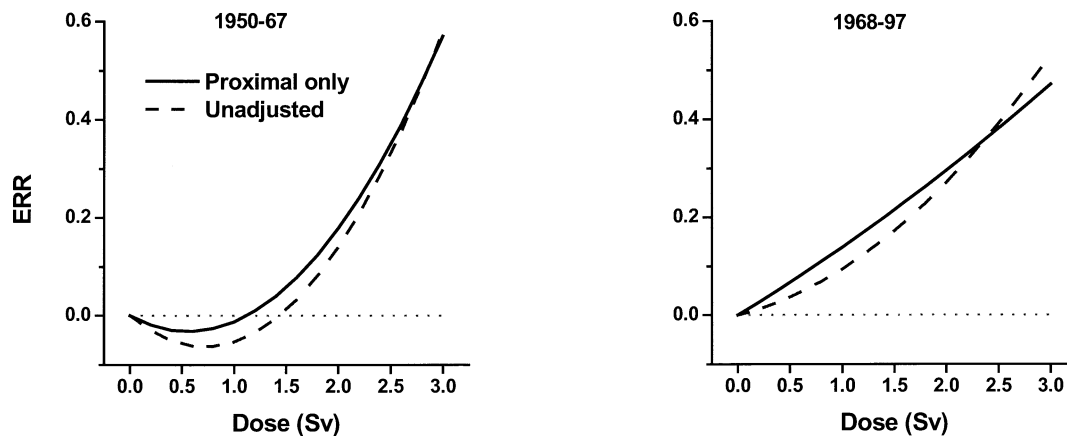


FIG. 9. Comparison of fitted noncancer mortality dose-response curves for early (1950–1967) and late (1968–1997) portions of the follow-up period. The solid curves are fits made using only proximal survivor data. The dashed curves are based on the data for the full cohort with no allowance for selection effects.

sidering their applicability to other populations and other types of radiation exposure.

Cause-specific risk estimates are examined in Section 4.4. As in the previous report, statistically significant radiation effects are seen for heart disease, stroke, respiratory diseases, and digestive diseases. The point estimates of the ERR per Sv for these diseases are similar to those for noncancer diseases as a group. There is no evidence of an effect of radiation on infectious disease rates or on the rate of all other noncancer diseases (excluding diseases of the blood).

4.1 Noncancer Disease Dose Response

The LSS data provide evidence of an association between radiation exposure and noncancer disease mortality. In earlier reports we have shown that neither misclassification of the cause of death (2, 35) nor confounding between non-radiation risk factors (e.g. smoking habits or proximal–distal differences in background rates) and radiation dose (2) can explain the association between radiation effect and noncancer risks. These issues will not be revisited in this report. However, as noted in ref. (2), characterization of the dose response is complicated by a “healthy survivor” selection effect on noncancer disease death rates. For a few years after the bombings, baseline (zero dose) noncancer disease death rates for proximal survivors (within 3 km of the hypocenters) were markedly lower than those for distal survivors. The difference diminished steadily over the first two decades of follow-up, by which time it had largely vanished. This statistically significant pattern, which has the nature of the classical “healthy worker” effect (36) often seen in occupational studies, suggests that proximal survivors included in the LSS were initially healthier than the general population for reasons related to their selection by having survived the bombings. In particular, analyses of the LSS noncancer mortality data indicate that in 1950 baseline death rates for proximal survivors were 15% lower than those for distal survivors. The difference decreased to about 2% in the late 1960s. This small,

but statistically significant, difference has persisted and is more likely to reflect demographic effects unrelated to the bombings, e.g. urban–rural differences, than the bomb-related selection effects seen during the early years of follow-up.

Unless allowances are made, a substantial healthy survivor selection leads to spurious curvature in the dose response. This is illustrated in Fig. 9. The dashed lines are fitted dose-response functions for the periods 1950–1967 and 1968–1997 with no allowance for selection effects. The nature of these fitted curves differs significantly ($P = 0.01$), with significant curvature in the early period ($P = 0.003$) and no significant non-linearity in the later period ($P > 0.5$). There are two relatively simple approaches to dealing with this difficulty: (1) restricting analysis to proximal survivors, or (2) restricting analysis to the later period and using the entire cohort. The solid lines in Fig. 9 are based on method (1). While, as expected, the degree of curvature in the pre-1968 period is reduced, there is still significant curvature ($P = 0.02$) in this period, but none in the later period ($P > 0.5$), with a statistically significant difference ($P = 0.01$) in the shape between the periods. Thus simply restricting attention to proximal survivors does not resolve differences between the early and later periods. Distance-dependent selection effects within 3 km of the hypocenter could explain much of the residual curvature in the dose response for the early period. Therefore, the primary noncancer risk estimates are based on analyses of data from the last three decades of follow-up, which is similar to the approach used in ref. (2). Results are presented with and without adjustment for the small proximal–distal baseline rate differences during this period.

Figure 10 presents fitted linear and smoothed dose-response curves for the period 1968–1997 with no adjustment for proximal–distal baseline rate differences. The linear regression was carried out on the full dose range without allowance for variation in the ERR with sex, age at exposure, attained age or other factors. While, as noted above,

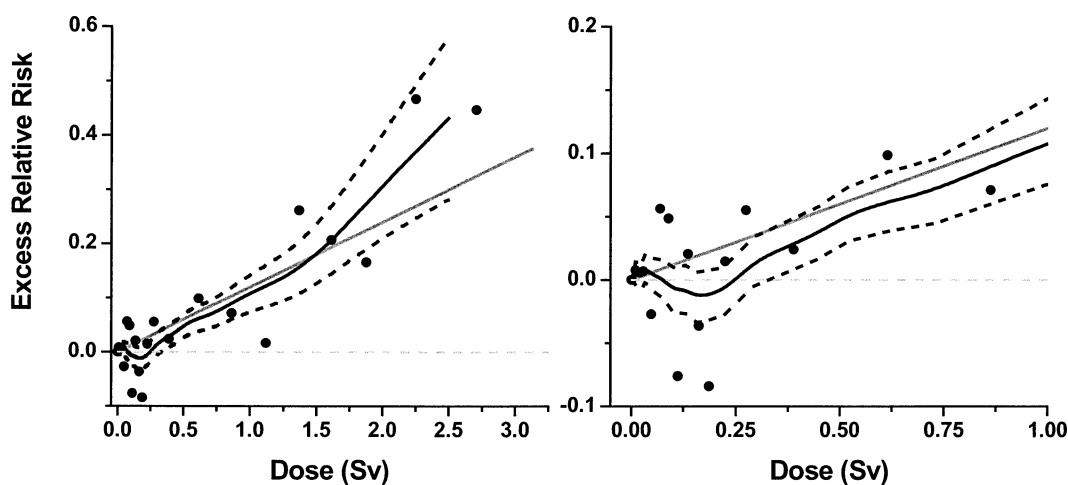


FIG. 10. Noncancer dose-response function for the period 1968–1997. The solid straight line indicates the fitted linear ERR model without any effect modification by age at exposure, sex or attained age. The points are dose category-specific ERR estimates, the solid curve is a smoothed estimate derived from the points, and the dashed lines indicate upper and lower one-standard-error bounds on the smoothed estimate. The right panel shows the low-dose portion of the dose-response function in more detail.

there is no indication of significant non-linearity in the dose response, the figure shows that there is considerable uncertainty regarding the dose-response relationship or even the existence of an effect at doses below about 0.5 Sv.

Table 11 presents parameter estimates, confidence intervals, and relative deviance changes for linear, linear-quadratic, and pure-quadratic dose-response models during the last 30 years of the follow-up period. The lower portion of this table gives estimates without adjustment for proximal-distal baseline differences (corresponding the full cohort analysis shown in Fig. 9), while the upper portion presents results based on the adjusted analyses (which is similar to proximal-only analyses in Fig. 9.)

A linear-quadratic dose-response model does not fit these data significantly better than a simple linear model, while a pure-quadratic model fits only slightly worse than the linear-quadratic model. Because of the higher baseline rate for distal survivors, the adjusting for proximal-distal differences in the baseline rates results in risk estimates that

are somewhat higher, with curvature estimates that are lower (about $0.027/0.09 = 0.3$ compared to $0.04/0.05 = 0.8$), decreased evidence for non-linearity ($P = 0.4$ compared to $P = 0.2$), and more evidence against a pure quadratic dose response than the unadjusted analyses.

Consideration of models with a threshold below which there is no radiation effect followed by a linear increase at higher doses provides no evidence against a threshold of zero ($P > 0.5$). The maximum likelihood estimate of the threshold in the adjusted analysis is about 0.15 Sv with an upper 90% confidence bound of about 0.55 Sv. Without allowance for proximal-distal difference analyses, the estimated threshold is about 0.2 Sv with an upper bound of about 0.7 Sv with no evidence ($P = 0.4$) against the linear no-threshold hypothesis. These results suggest that radiation effects on LSS noncancer mortality 25 or more years after exposure can be adequately described by a linear dose-response model with risk increases of about 14% per Sv as indicated in the top line of Table 11.

TABLE 11
Noncancer Dose-Response Parameter Estimates for the Period of 1968–1997

Dose-response model	Parameter estimates		Deviance change ^a
	Linear	Quadratic	
With proximal–distal adjustment			
Linear	0.14 (0.09; 0.19)	0	0.65
Linear quadratic	0.09 (−0.01; 0.20)	0.027 (−0.03; 0.085)	0
Quadratic	0	0.71 (0.04; 0.10)	2.0
Without proxima–distal adjustment			
Linear	0.12 (0.07; 0.17)	0	1.6
Linear-quadratic	0.05 (−0.05; 0.15)	0.04 (−0.01; 0.10)	0
Quadratic	0	0.07 (0.04; 0.10)	0.8

^a Deviance change from linear-quadratic model. Values greater than 3.84 indicate a statistically significant ($P < 0.05$) lack of fit for the simpler (linear or quadratic) models.

TABLE 12
Noncancer Dose–Response Parameter Estimates for the Period of 1950–1967

Dose–response model	Parameter estimates		Deviance change ^a
	Linear	Quadratic	
Proximal only			
Linear	0.05 (–0.02; 0.13)	0	5.3
Linear-quadratic	–0.12 (–0.3; 0.04)	0.10 (0.02; 0.19)	0
Quadratic	0	0.05 (0.00; 0.09)	2.2

^a Deviance change from linear-quadratic model. Values greater than 3.84 indicate a statistically significant ($P < 0.05$) lack of fit for the simpler (linear or quadratic) models.

Table 12 documents the fit shown in the left panel of Fig. 9, which is of some interest but does not bear directly on the primary risk estimation used here. The data for the first two decades after exposure suggest a non-linear dose response even after some basic adjustments for apparent selection effects during this period. As noted earlier, this is likely to be, at least in part, an artifact of distance-dependent selection effects on baseline noncancer disease rates for proximal survivors that are not accounted for by adjustments based on simple proximal–distal comparisons. Parameter estimates for various dose–response models for the first 17 years of follow-up are presented in Table 12. These models were fitted to all of the data with a time-dependent adjustment for selection effects. Either the linear-quadratic or pure-quadratic models would seem to provide adequate descriptions of the early LSS data. However, since distance-dependent selection effects among proximal survivors are likely to bias the dose–response parameter estimates for this period, generalization to other populations or different exposure situations is probably unwarranted.

4.2 Age-at-Exposure, Age and Sex Effects

For analyses of the effects of temporal patterns, age at exposure, and sex on the noncancer excess risks, we focused on the last period of follow-up and considered linear dose–response models. Because the noncancer ERR is considerably less than that for solid cancer and background rates are higher, precise characterization of effect modification is even more difficult than for cancer. Generally speaking the age patterns and sex effects on the noncancer risks are similar to those seen for solid cancers, but, as discussed below, none of the factors considered exhibit statistically significant effects.

We estimate that the ERR decreases by 15% (90% CI 36% decrease to 11% increase) per decade increase in age at exposure, with the estimated risk for exposure at age 30 being 0.15 (90% CI 0.10; 0.21). This trend, which is about half as large as that seen for solid cancer, was not statistically significant. The difficulties in interpreting or generalizing from age-at-exposure effects in the LSS, noted in the discussion of solid cancer risks, also apply to noncancer excess risks. Indeed, since the birth cohort effects and secular trends in noncancer disease mortality are generally greater than those for cancer, the problem is likely to be

even more pronounced for noncancer diseases. However, as for solid cancer, we feel that useful insights can be gained through the consideration of the effect of age at exposure and other factors on excess rates, as described later in this section.

We also considered a description in which the noncancer ERR was allowed to vary (only) with attained age. The noncancer ERR exhibits a nonsignificant decrease with increasing attained age that is proportional to age to the -0.7 power (90% CI -1.9 ; 0.8) with an estimated ERR per Sv at age 70 of 0.14 (90% CI 0.09; 0.19).

The estimated ERR per Sv for men (0.11, 90% CI 0.04; 0.18) is 65% of that for women (0.17, 90% CI 0.10; 0.24). This difference is not statistically significant ($P = 0.3$). However, the sex ratio seen in the ERR is similar to that for solid cancer and can likewise be interpreted as largely offsetting sex differences in background rates.

The simplest useful EAR model is one in which the EAR is allowed to increase with increasing attained age with no variation with either age at exposure or sex. Under this model the estimated EAR per Sv at age 70 is 22.3 radiation-associated deaths per 10,000 PY-Sv (90% CI 14; 31), and it increases in proportion to age to the power 5.6 (90% CI 3.5; 8.2). This model fits somewhat better than the constant ERR model (the deviance difference for these non-nested models is 5.2) or ERR models with sex, attained age, or age-at-exposure effects. There are no indications of significant age-at-exposure ($P = 0.4$) or sex effects ($P > 0.5$) on the EAR.

The left panel in Fig. 11 summarizes the age dependence in various fitted ERR models, while the right panel contrasts the basic EAR model with the model in which the EAR is also allowed to have a log-linear dependence on age at exposure.

4.3 Lifetime Risk Estimates

Because of the greater uncertainty about nature of both the shape of the radiation dose response and how the effect varies with sex, age and age at exposure, we consider sex-specific lifetime risk estimates for three different risk models: (a) the constant ERR model, (b) an alternative ERR model with age-at-exposure and sex effects, and (c) an EAR model with no sex or age-at-exposure effects. Because the existence of effects at low doses is less clear than for

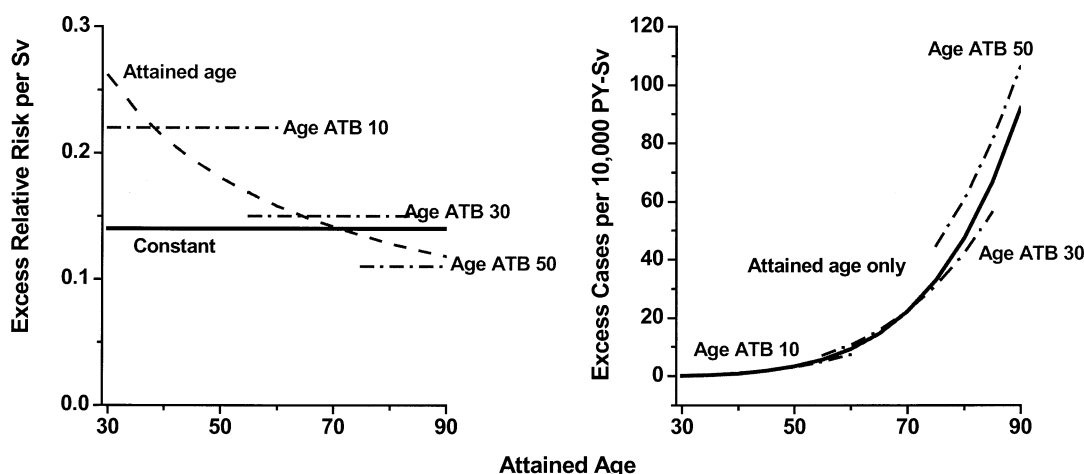


FIG. 11. Fitted noncancer ERR and EAR models. The ERR models shown in the left panel include a constant ERR model (solid line) and alternatives in which the ERR varies with either attained age (light dashed curve) or age at exposure (dashed-dotted lines). As described in the text, neither the attained age nor age-at-exposure effects significantly improve the fit. The EAR models (right panel) include a basic description in which the EAR increases in proportion to age power (dark curve) and a model in which the EAR is also allowed to depend on age at exposure (dash-dotted curves).

solid cancer, we present estimates of the effect of an exposure to 1 Sv. Uncertainty about the shape of the dose response has little impact on risk estimates for doses ranging from 1 to 2 Sv, but it is increasingly important at lower doses.

Lifetime risk and life-lost estimates were computed using lifetable methods and include noncancer disease deaths that were hastened by exposure. Figure 12 provides a graphical summary of sex-specific estimates of lifetime risk as a function of age at exposure. The parameter estimates used for these analyses were based on linear dose-response models fitted to the 1968–1997 follow-up data with adjustment for proximal–distal differences. The ERR per Sv estimate for the constant ERR model is 0.14 (Table 11). Under the alternative ERR model the ERR estimates after exposure at age 30 are 0.11 for men and 0.20 for women, and they decrease by about 20% per decade increase in age at exposure. The EAR model used was described earlier. Under this model, the increase in the EAR with age is proportional to age to the power 5.6 with no effects from either age at exposure or sex. The computations allow for the competing risk of solid cancer (including radiation effects) and other causes of death and assume a 5-year latent period. The years of life lost per radiation-associated death are similar for all three models, averaging about 8 years for exposure under age 50.

The lifetime risk estimates based on the constant ERR model are insensitive to age at exposure. This pattern, standing in marked contrast to that seen for solid cancer (Fig. 6), reflects both the time-constant ERR and the rapid decline in age-specific noncancer disease death rates that has taken place in Japan over the past 50 years. (That is, at the time people who were 50 years old in 1945 were dying, age-specific death rates were considerably greater

than they are for those exposed earlier in life who have been dying in recent years.) For either the age-at-exposure-dependent ERR or the EAR model, lifetime risks decrease with increasing age at exposure. Under a model with a sex-dependent ERR, women have about twice the risk seen for men. Generally, it appears that for those exposed as children, the noncancer lifetime risks may be around half of those for solid cancer (cf. Fig. 12 with the solid cancer estimates given in Table 7 and Fig. 6), while for people exposed at age 50 they may be about equal to those for solid cancer.

The calculations were made with the assumption of a 5-year minimum latent period and the assumption that the significant difference in the shape for the period 1950–1967 and 1968–1997 was due solely to selection effects. However, it is possible that other factors play a role in these differences. Assuming a 20-year latent period is a fairly simple way to assess the impact of differences in the nature of the dose response for the early and late portions of the follow-up period. Changing to a 20-year latent period has almost no effect on the estimated lifetime risks for those exposed under age 40, because noncancer disease death rates are low during the latent period. However, for those who were 50 at the time of exposure, this change decreases the lifetime risk estimates by about 30%. Radiation-associated noncancer disease risks for those exposed as children are lower than solid cancer excess risks, but somewhat greater for those exposed in middle ages.

4.4 Cause-Specific Risks

Table 13 presents, for selected noncancer disease cause-of-death groups, estimates of the ERR per Sv based on linear dose-response models fitted to the 1968–1997 fol-

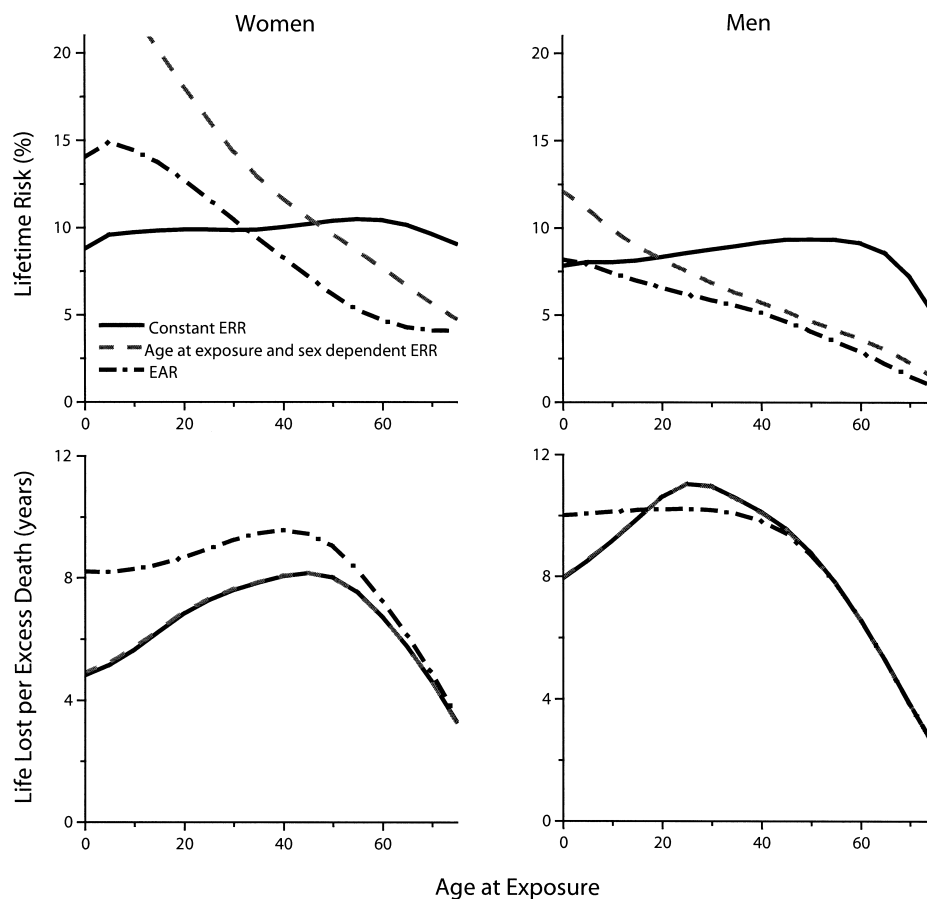


FIG. 12. Estimates of LSS noncancer disease lifetime risk and years of life lost per excess death by age at exposure and sex, and for a 1-Sv exposure. Estimates are based on constant ERR (dark solid lines) and age-at-exposure and sex-dependent (light dashed lines) ERR models and an EAR model (dark dashed-dotted lines). The parameter estimates for these models are described in the text and the estimated excess risks were plotted in Fig. 11.

TABLE 13
Life-Span Study Cause-Specific Noncancer Disease ERR Estimates 1968–1997

Cause	ERR per Sv	Deaths ^a	Estimated number of radiation-associated deaths
All noncancer diseases (0–139, 240–279, 290–799)	0.14 (0.08; 0.2) ^b	14,459	273 (176; 375) ^b
Heart disease (390–429)	0.17 (0.08; 0.26)	4,477	101 (47; 161)
Stroke (430–438)	0.12 (0.02; 0.22)	3,954	64 (14; 118)
Respiratory disease (460–519)	0.18 (0.06; 0.32)	2,266	57 (19; 98)
<i>Pneumonia</i> (480–487)	0.16 (0.00; 0.32)	1,528	33 (4; 67)
Digestive disease (520–579)	0.15 (0.00; 0.32)	1,292	27 (0; 58)
<i>Cirrhosis</i> (571)	0.19 (–0.05; 0.5)	567	16 (–2; 37)
Infectious disease (0–139)	–0.02 (<–0.2; 0.25)	397	–1 (–14; 15)
<i>Tuberculosis</i> (010–018)	–0.01 (<–0.2; 0.4)	237	–0.5 (–2; 13)
Other diseases ^c (240–279; 319–389, 580–799)	0.08 (–0.04; 0.23)	2,073	24 (–12; 64)
<i>Urinary diseases</i> (589–629)	0.25 (–0.01; 0.6)	515	17 (–1; 39)

^a Deaths among proximal survivors between 1968 and 1997.

^b 90% confidence interval.

^c Excluding diseases of the blood and blood-forming organs.

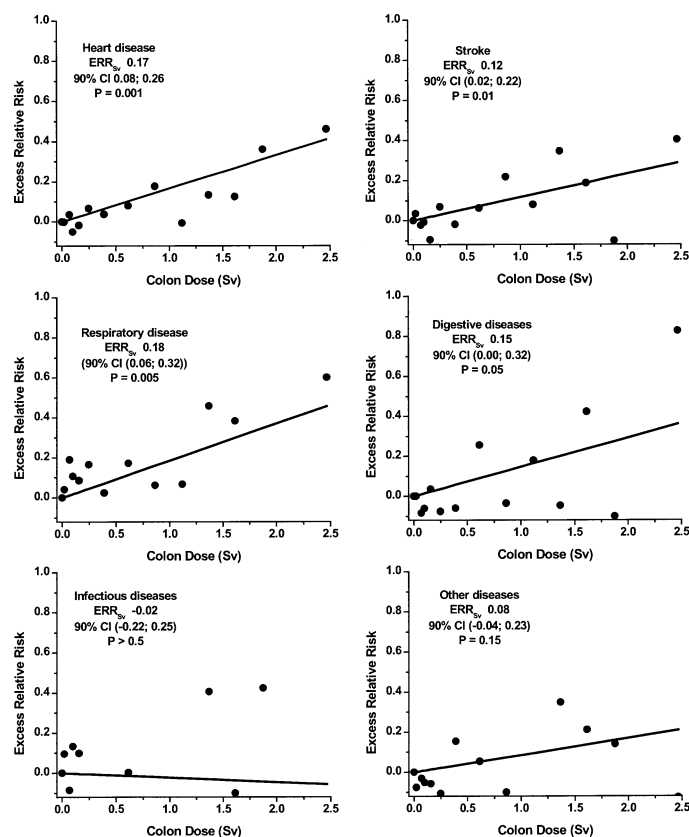


FIG. 13. Cause-specific dose-response functions for noncancer deaths. The plots display the best-fitting linear ERR models together with non-parametric ERR estimates for 20 dose categories.

low-up data. As in ref. (2), significant excess risks are seen for heart disease, stroke, respiratory diseases, and digestive diseases, while there is no indication of excess risks for infectious diseases. This table provides risk estimates for the more common causes of death within some of these groups. While there is no indication of statistically significant risks in any of the more detailed subgroups, the number of cases is relatively small for these more specific causes, so that detection of effects of the order of 10 to 20% per Sv is difficult. However, the ERR estimates are generally similar to what one would expect on the basis of the results for the diseases with larger numbers of deaths.

The nature of the dose-response relationships for cause-specific risks for six categories of noncancer disease deaths are shown in Fig. 13, in which we present the fitted linear slope estimates along with ERR estimates for 20 dose categories. (The highest dose category in these plots was taken to be 2 Sv or more.)

As noted earlier in this section, noncancer diseases of the blood and blood-forming organs were excluded from these analyses because there are indications that radiation-associated risks for the 222 deaths due to these causes are considerably higher than those for other noncancer diseases (or solid cancer). Blood disease mortality risks were discussed in detail in (2). With the extended follow-up data, we estimate the ERR per Sv for blood diseases over the last 30

years of follow-up to be 1.9 (90% CI 1.0; 3.2), with a suggestion ($P = 0.08$) of variation in the ERR with age at exposure and no indication of either attained-age ($P > 0.5$) or sex ($P > 0.5$) effects.

5. DISCUSSION

5.1 Generalization from LSS Risk Estimates

As we have indicated throughout this report, the difficulty in interpreting radiation age-at-exposure effects is an important issue. On a site-specific basis, these effects cannot be disentangled from birth cohort trends in background rates without knowing whether radiation acts more additively or multiplicatively with respect to the causes of those trends. This difficulty is more serious than is immediately apparent when considering all solid cancers together, since the lack of a substantial birth cohort trend is due to the canceling out of large trends in opposite directions for major cancer sites. In this report we have pointed out these difficulties without trying to resolve them, but further progress on the issue will be important. We believe that there are approaches that can help resolve this issue. First, the discussion and interpretation of age-at-exposure effects has in the past focused largely on those seen in the ERR, but the corresponding effects on EARs deserve more attention, since the ERR-EAR comparisons provide important clues about the nature of the effects. For example, the pattern seen for stomach cancer (Fig. 7) provides some indication that radiation is acting additively with regard to the major factors responsible for the birth cohort effects in LSS background stomach cancer mortality rates. Furthermore, it seems likely that comparisons with cancer incidence data will generally be more informative than those indicated here for cancer mortality. The ideal aim is understanding some *bona fide* biological effect which is presumably independent of whether one considers mortality or incidence data, or whether one arbitrarily considers effects seen in the ERR or EAR. A more limited but perhaps more realistic goal focuses on how one should generalize from the LSS to other populations and other periods in which there are different birth cohort trends (or period effects) than have been seen in the LSS.

It is natural to be concerned about whether or not LSS-based risk estimates are biased as a result of selection by survival. We have identified and dealt with such selection effects on the noncancer risk estimation. There has been prominent and justifiable concern regarding whether or not LSS-based cancer risk estimates could be biased by selection effects (37–40). We consider it important progress on this issue that the same statistical methods used for identifying bias for noncancer mortality provide no such evidence for cancer mortality. The fact that there is a rather marked selection effect on noncancer disease death rates does not imply the existence of selection effects on cancer death rates or bias in cancer risk estimates. For early mor-

tality selection to cause appreciable bias in cancer risk estimation would require strong correlations between the individual sensitivities for cancer and early mortality. The degree of correlation required for a serious bias seems to us implausible. We are investigating these issues and will discuss them further in future papers.

While continuing developments of mechanistic models for radiation carcinogenesis (23–25, 41–43) provide insights for modeling and interpreting LSS results, this report relies explicitly only on empirical descriptions of the radiation effects, including variations with dose, sex, age at exposure, and attained age. These descriptions involve empirically based mathematical models, of which the form and fitted values have been reasonably stable as the follow-up period increases. These models are hence useful for predictions regarding the future of the LSS cohort, and the greatest uncertainties involve generalizations from this cohort to other cultures, time periods, and types of radiation exposure. There is further uncertainty, however, in the interpretation of particular parameter estimates in these models, for example in distinguishing between effects of age at exposure, attained age, and birth cohort variations in background cancer rates.

5.2 Relationship to Other Studies

As recently reviewed by UNSCEAR (18), information about radiation effects on solid cancer risks is available from a number of studies involving medical, occupational and environmental exposures. In medical and many occupational studies, exposures are largely localized to certain organs. Thus, while few other studies provide risk estimates for all solid cancers, site-specific results from other studies are, with a few exceptions, generally consistent with the LSS. These other studies provide information that cannot be obtained from the LSS, including effects of dose fractionation (44, 45), protraction (46), and exposures to high-LET radiation (47), and they allow for comparisons between populations with different baseline cancer rates (28, 48). One of the most striking contrasts to the LSS findings concerns lung cancer among tuberculosis patients who received highly fractionated doses from repeated fluoroscopic examinations (45, 49) among whom there are no indications of elevated risks. In these cohorts, which involve lengthy follow-up and considerable numbers of cases, there are no apparent increases in lung cancer risks while excess rates for female breast cancer in these cohorts are increased similarly to the LSS.

Many reports attempt to address the question of which description of the excess risk (relative risks or excess rates) derived from one population is most appropriate for application to another (18, 28, 46, 48, 50). A major goal of these studies concerns how LSS risk estimates might be applied to other populations, but the results indicate that there is no simple answer to this question. For breast cancer (28, 44, 51, 52), it has been suggested that LSS (age-dependent)

EAR might best be used to estimate risks in other populations, while for other sites, including stomach (50) and thyroid (48), it has been suggested that the ERR might be the most appropriate for this purpose. In this report we have made some attempts to contrast patterns of age-at-exposure effects on the ERR and EAR for various sites. Such comparisons should eventually help to provide understanding of how LSS risks estimates might best be applied to non-LSS populations, but more work needs to be done in this area.

The LSS continues to provide strong evidence that mortality rates for noncancer disease in atomic bomb survivors increase with increasing dose, and it suggests that the total impact of these effects in the LSS may be roughly comparable to that seen for solid cancer. There are compelling indications that these risks are elevated even at doses below 1 Sv. While there is considerable uncertainty about the shape of the dose response in the low-dose range, and in particular little direct evidence of risk below about 0.5 Sv, the LSS data are not inconsistent with linearity over this range. As in our previous report (2), the primary analyses focused on noncancer diseases as a group. More detailed examination of the data indicates that elevated risks are seen for several broad categories of noncancer disease deaths, including stroke, heart disease, and respiratory diseases, but provides little evidence of elevated risks for others such as infectious diseases or diseases of the endocrine or nervous systems. While the general nature of the increase and the lack of understanding of possible mechanisms naturally raises concerns about causality, the LSS findings cannot be dismissed on this basis alone. Although epidemiological and experimental data are limited, a number of studies suggest the possibility of radiation effects on some non-cancer diseases.

Radiation-induced heart disease is manifested primarily as pericardial lesions related to high-dose irradiation ranging from 40 to 60 Gy, depending on the size of irradiated heart volume (53, 54). It was recognized in the 1960s when excess heart disease mortality was observed after radiotherapy for Hodgkin's disease and other cancers (55). More recent data have also demonstrated an excess risk of myocardial infarction or coronary heart disease among patients who received radiotherapy for Hodgkin's disease (56, 57) and breast cancer (58–64).

At somewhat lower doses, an increase in noncancer disease mortality was seen in the British study of ankylosing spondylitis patients (65), but the authors dismissed this as being a likely consequence of the disease itself. Higher than expected mortality from heart disease has been found in patients who received radiotherapy for peptic ulcer (66) and metropathia hemorrhagica (67, 68). For the peptic ulcer patients, there was speculation that less fit subjects were selected for radiotherapy. However, recent analyses of updated data find a statistically significant increase of 10% per Sv in the coronary heart disease relative risk after adjustment for smoking and other risk factors (Carr, personal

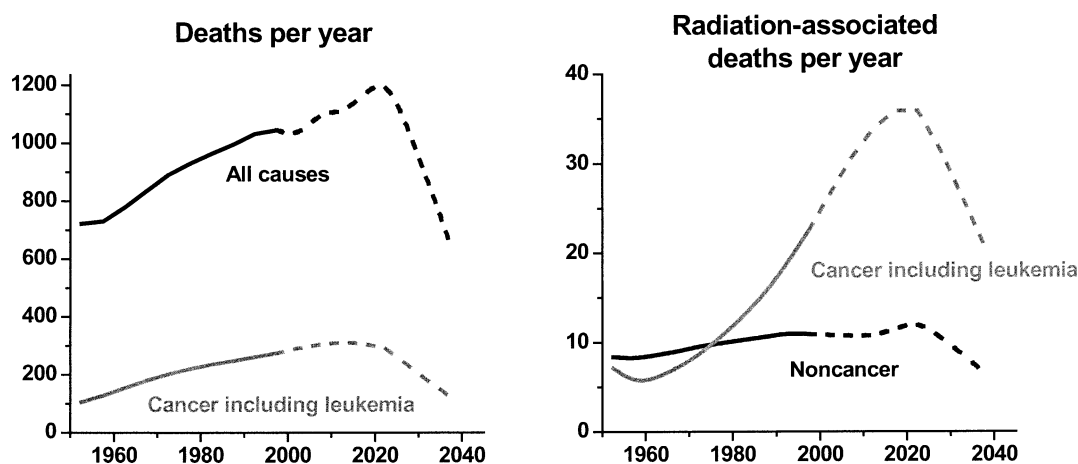


FIG. 14. Total and radiation-associated deaths per year for all causes and for cancers including leukemia. The solid lines show the data for the 1950 through 1997 follow-up period while the dashed lines are projections based on the primary ERR models discussed in this paper. The solid cancer model includes both age-at-exposure and attained-age effects while the linear constant relative risk model was used for noncancer. Background rates were projected assuming the birth cohort effects seen in the cohort to date will continue into the future. Assuming no future changes in background rates has little impact on the nature of the plot.

communication, submitted for publication). Increased heart disease risks were not seen among tuberculosis patients who received multiple chest fluoroscopy (69).

Studies of occupational cohorts, which are often hampered (as a result of low doses) by limited power to detect effects, a lack of reliable dosimetry, or a paucity of information on confounding factors, have not provided clear evidence for or against radiation-associated increases in noncancer mortality. A U.S. study of radiologists (70) reports an increase in cardiovascular disease rates in comparison with those for physicians in other fields. More recently, increased mortality from circulatory disease has been found among radiological technologists who worked in early years when radiation exposures were high, and this excess was significant after adjusting for several possible confounders (71). On the other hand, similar increases have not been seen in a long-term study of UK radiologists (72). Analysis of pooled data from nuclear industry workers in Canada, the United Kingdom and the United States showed a significant association between mortality from circulatory disease and radiation doses (46). Similar effects have also been seen in more recent analyses of UK nuclear workers (73) and Chernobyl clean-up workers (74). However, as noted by the authors of these reports, the possibility that the observed associations are attributable to confounding by lifestyle factors cannot be ruled out. A study of Japanese nuclear workers (75) has found no significant effect for noncancer diseases, but the study has considerable limitations and also finds no significant effect for solid cancer mortality.

Clinical and laboratory studies on a subset of the LSS cohort provide evidence supplementing the mortality results that radiation dose is associated with the incidence of cardiovascular disease, stroke, chronic liver disease, and various other diseases (76–78). In addition, subtle long-term

radiation effects in the survivors have been reported for a number of precursors of noncancer disease, including aortic arch calcification (79) and isolated systolic hypertension (80), changes in the age trends for cholesterol (81) and blood pressure (82). Recent work has also provided evidence of persistent radiation-associated imbalances in the survivors' immune systems (83) and subclinical inflammation (84, 85), which may pertain to mechanisms for radiation effects on a broad spectrum of noncancer diseases. The LSS noncancer findings highlight the need for additional studies that could help to identify or refute possible mechanisms for radiation effects on noncancer disease rates.

5.3 Future Course of LSS Cancer Mortality

As shown in Table 1, about half of the LSS cohort members were alive at the end of the current follow-up. This fact combined with the apparent lifelong radiation-associated increase in cancer and noncancer risks seen in the cohort suggests that there will be considerable additional epidemiological information on radiation effects on mortality in the LSS. Figure 14 describes the course of the study to date and makes predictions about the future course of mortality in the LSS. This was done using the solid cancer and noncancer ERR models developed from our current analyses and the leukemia mortality model described in LSS Report 12 (1).

The left panel presents the estimates of the observed number of deaths per year for all causes and for all cancers (including leukemia) among the portion of the LSS cohort used in these analyses (that is, the estimates refer to the cohort 86,572 LSS cohort survivors for whom dose estimates are available). Recently about 1000 cohort members have died each year, and about 280 of these deaths were

attributed to cancer. Because people exposed prior to age 20 comprise the largest portion (41%) of the cohort and most of these are still alive, the total number of deaths and cancer deaths each year will continue to increase for the next 15 years or so, rising to about 1225 deaths and 310 cancer deaths per year. The right panel presents information on the number of radiation-associated deaths per year for cancer (including leukemia) and all causes. Toward the end of the current follow-up, we estimate there were about 35 radiation-associated deaths per year, of which about 23 are due to cancer. The number of radiation-associated deaths per year can be expected to increase over the next 15 years, increasing to about 45 per year for all causes and 36 per year for cancer.

Because our risk models suggest that excess rates (particularly for cancer) are highest for those exposed as children, we anticipate that 60 to 70% of the radiation-associated deaths in the LSS cohort have yet to occur. Although there is uncertainty in the projections, they clearly indicate

that basic epidemiological analyses of the LSS will continue to provide important new insights into the nature of radiation effects for several more decades. In addition, as continuing programs to collect, store and analyze biological materials for the survivors are improved, the LSS is likely to become an even more useful resource for the quantification and understanding of radiation effects on humans.

APPENDIX: SUMMARY ESTIMATES OF SOLID CANCER SITE-SPECIFIC RISKS

The following tables provide site-specific summary risk estimates based on organ-specific survivor dose estimates. These estimates are based on age-constant ERR models with site-specific age-at-exposure effects for major sites where these can be reasonably estimated, and the reported ERR is for age at exposure 30. For minor sites, this effect is set to zero. The summary EAR estimate is the ratio of the estimated number of excess deaths to the total PY-Sv. The cohort attributable risk is the estimated number of excess deaths divided by the number of deaths among those whose estimated dose is at least 5 mSv.

TABLE A1
LSS Male Site-Specific Summary Mortality Risk Estimates: Solid Cancers 1950–1997

Site/system	Deaths (≥ 0.005 Sv)	ERR/Sv ^a (90% CI)	EAR/10 ⁴ PY-Sv ^b (90% CI)	Attributable risk (%) ^c (90% CI)
<i>All solid cancer</i>	4,451 (2554)	0.37 (0.26; 0.49)	12.6 (9.4; 16.2)	6.6 (4.9; 8.4)
<i>Oral cavity</i>	68 (37)	-0.20 (<-0.3; 0.45)	-0.12 (<-0.3; 0.25)	-5.2 (<-6; 11)
<i>Digestive system</i>				
Esophagus	224 (130)	0.61 (0.15; 1.2)	1.1 (0.28; 2.0)	11.1 (2.8; 21)
Stomach	1,555 (899)	0.20 (0.04; 0.39)	2.1 (0.43; 4.0)	3.2 (0.07; 6.2)
Colon	206 (122)	0.54 (0.13; 1.2)	1.1 (0.64; 1.9)	12 (6.9; 21)
Rectum	172 (96)	-0.25 (<-0.3; 0.15)	-0.41 (<-0.4; 0.22)	-5.4 (<-6; 3.1)
Liver	722 (408)	0.39 (0.11; 0.68)	2.4 (1.2; 4.0)	8.4 (4.2; 14)
Gallbladder	92 (52)	0.89 (0.22; 1.9)	0.63 (0.17; 1.2)	17 (4.5; 33)
Pancreas	163 (103)	-0.11 (<-0.3; 0.44)	-0.15 (<-0.4; 0.58)	-1.9 (<-6; 7.5)
<i>Respiratory system</i>				
Lung	716 (406)	0.48 (0.23; 0.78)	2.7 (1.4; 4.1)	9.7 (4.9; 15)
Prostate	104 (53)	0.21 (<-0.3; 0.96)	0.18 (<-0.2; 0.75)	4.9 (<-5; 20)
<i>Urinary system</i>				
Bladder	83 (56)	1.1 (0.2; 2.5)	0.7 (0.1; 1.4)	17 (3.3; 34)
Kidney	36 (18)	-0.02 (<-0.3; 1.1)	-0.01 (-0.1; 0.28)	-0.4 (<-5; 22)
<i>Brain/CNS</i>	14 (9)	5.3 (1.4; 16)	0.35 (0.13; 0.59)	62 (23; 100)

^a ERR/Sv for age at exposure 30 in an age-constant linear ERR model.

^b Average EAR computed from ERR model.

^c Attributable risk among survivors whose estimated dose is at least 0.005 Sv.

TABLE A2
LSS Female Site-Specific Summary Mortality Risk Estimates: Solid Cancers 1950–1997

Site/system	Deaths (>0.005 Sv)	ERR/Sv ^a (90% CI)	EAR/10 ⁴ PY-Sv ^b (90% CI)	Attributable risk (%) ^c (90% CI)
<i>All solid cancer</i>	4,884 (2,948)	0.63 (0.49; 0.79)	13.5 (7.4; 16.3)	9.2 (7.4; 11.0)
<i>Oral cavity</i>	42 (25)	−0.20 (<−0.3; 0.75)	−0.04 (<−0.3; 0.14)	−4.1 (<−6; 14)
<i>Digestive system</i>				
Esophagus	67 (44)	1.7 (0.46; 3.8)	0.51 (0.15; 0.92)	22 (6.6; 42)
Stomach	1,312 (786)	0.65 (0.40; 0.95)	3.3 (2.1; 4.7)	8.8 (5.5; 12)
Colon	272 (150)	0.49 (0.11; 1.1)	0.68 (0.76; 1.3)	9.0 (3.4; 17)
Rectum	198 (127)	0.75 (0.16; 1.6)	0.69 (0.16; 1.3)	11.3 (2.6; 22)
Liver	514 (291)	0.35 (0.07; 0.72)	0.85 (0.18; 1.6)	6.2 (1.3; 12)
Gallbladder	236 (149)	0.16 (−0.17; 0.67)	0.18 (−0.21; 0.71)	2.6 (−2.9; 10)
Pancreas	244 (135)	−0.01 (−0.28; 0.45)	−0.01 (−0.35; 0.52)	−0.2 (−5.0; 7.6)
<i>Respiratory system</i>				
Lung	548 (348)	1.1 (0.68; 1.6)	2.5 (1.6; 3.5)	16 (10; 22)
Female breast	272 (173)	0.79 (0.29; 1.5)	1.6 (1.2; 2.2)	24 (18; 32)
Uterus	518 (323)	0.17 (−0.10; 0.52)	0.44 (−0.27; 1.3)	2.7 (−1.6; 7.9)
Ovary	136 (85)	0.94 (0.07; 2.0)	0.63 (0.23; 1.2)	15 (5.3; 28)
<i>Urinary system</i>				
Bladder	67 (43)	1.2 (0.10; 3.1)	0.33 (0.02; 0.74)	16 (0.9; 36)
Kidney	31 (21)	0.97 (<−0.3; 3.8)	0.14 (<−0.1; 0.42)	14 (<−3; 42)
<i>Brain/CNS</i>	17 (10)	0.51 (<−0.3; 3.9)	0.04 (<−0.02; 0.2)	11 (<0.05; 57)

^a ERR/Sv for age at exposure 30 in an age-constant linear ERR model.

^b Average EAR computed from ERR model.

^c Attributable risk among survivors whose estimated dose is at least 0.005 Sv.

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